M61-2

Tuskegee Syphilis Study Ad Hoc Advisory Panel

Charge III Subcommittee*

December 18, 1972

Panel Members Present:

Dr. Broadus N. Butler, Chairman of Panel

Dr. Jay Katz, Chairman of Subcommittee

Mr. Ronald Brown

Dr. Seward Hiltner

DHEW Staff Present:

Dr. Ernest Allen

Dr. Robert W. Berliner

Dr. Donald T. Chalkley

Dr. Thomas C. Chalmers

Dr. Irwin J. Kopin

Dr. R. W. Lamont-Havers

Dr. Carl M. Leventhal

Mr. Joel Mangel, Esq.

Dr. Sheldon M. Wolff

Panel Staff Present:

Dr. Robert C. Backus

Mrs. Bonnie M. Lee

Mr. James Morant

Mr. Robert Rawles

(Quotations are not always correctly attributed.)*

DR. BACKUS:

I think you all have copies of the memoranda we sent out, and you know that we are here concerned with the Third Charge given to the Panel by Dr. DuVal. We have indicated that this has two parts. To determine whether existing policies to protect the rights of patients participating in health research conducted by the DHEW are adequate and effective; and to determine whether existing policies to protect the rights of patients participating in health research supported by the DHEW are adequate and effective; and then to recommend improvements in these policies, as needed. We are concerned at the early part of this meeting with the conducted aspects of the DHEW program; that means the intramural programs. I have asked Dr. Chalmers, who has a sizeable responsibility in this area as the Director of the Clinical Center, to lead off with some comments and give us a general picture as to how it has developed here at the Clinical Center over the years. Perhaps you can indicate some further developments in the policy on protection of human subjects within the Clinical Center and the NIH in general.

DR. CHALMERS:

I am going to open with a few introductory remarks about the philosophy of research on humans as we look at it here in the Clinical Center. I do this partly to help you understand something about the organization of the NIH. The Clinical Center is here to service the Institutes. They are responsible for conducting research by whatever means is best to answer their questions. And when they conduct that research with patients, it is our responsibility to care for the patients in the best possible way to be sure that the clinical research is entirely exemplary, excellent, and safe. As Director of the Clinical Center I have some responsibility for that with the Clinical Directors of each of the Institutes. I also have an appointment as Associate Director of the NIH for Clinical Care. In that job I have some responsibility for standards and controlled clinical trials that are supported by the intramural program under contracts. There are also a few related grant supported studies. Because of my long standing interest in clinical trials, I am involved in that and have represented Dr. Marston in some of the problems and discussions and also have served on the Policy Advisory Board of a number of clinical trials that are now going on. I have a special interest

in this field in determining how one practices the best possible medicine in the environment of research and the best possible research in the environment of practice. In other words, in developing the concept that each can be highly superior if the other is actively being pursued.

I have put on the board a few definitions. Although you may have heard them all before now, and if you have been through Dr. Katz' book, I am sure you've seen and heard these, I think it is worthwhile emphasizing them again. One I think is not emphasized enough is the distinction between practice and research; or rather, really, the lack of distinction between practice and research. I've pursued my present career goals for the last 25 years because after 6 years of practicing internal medicine, I found it entirely unsatisfactory. I realized that most of the time I didn't realize what I was doing, and I often found that I had been doing the wrong thing, and that my contemporaries were doing the wrong thing; sometimes quite serious wrong things. We thought they were right at the time. The evidence indicated that they were right at the time, but then somebody did a better study or a new study and showed it was wrong. I think that this emphasizes the fact that the word practice is just what it means. The doctor is practicing on his patient according to his best available standards, but it is not really that different from research. As we observe what goes on here where every patient comes into the hospital for research, we find that we are practicing medicine a lot and that in regard to such important things as informed consent, we really can't distinguish between practice and research. Practice should have the same high standards of informed consent as research has.

Now the risk/benefit ratio; we hear about it all of the time; and it seems to me that the best way to remind ourselves of what we are talking about is to construct a matrix in which risk is rated from none to slight to definite, and benefit from none to slight to definite; and then if you mentally classify studies this matrix is useful. You would never want to do a study that had no risk if it also had no benefit. I would also like to add that we should not solely talk about benefits to the individual, but should talk about benefits to the individual and to society. And then, since it has not been done enough in the past, we should talk about risk of any study to the individual and to society. A badly designed study which results in bad publicity for medical

research is, I think, a study that has great risk to society as well as any risk it may have had to the individual. So there are no studies, ideally, that have no benefit and no risk to either society or the individual; and there are certainly none that have no benefit and definite risk or slight risk. But where the benefit to society or the individual begins to be appreciable then one tends to move a little bit toward slight or even in some cases definite risk with a greater feeling of fulfilling ones responsibility towards both the patient and society.

The distinction between the volunteer and the involunteer is, I think, important in all of these, both in practice and in research, and I think that it is well to consider these separately from the distinction between well and sick. Sometimes one is inclined to think of a normal volunteer as being different from a sick patient. But in fact a sick patient is also a volunteer when he is having research done on him. A sick patient can actually be similar to a normal volunteer in the degree to which he benefits from that research in that he may be volunteering for something that is not directly applied to his own research. Similarly quite often research is done in sick patients in which they are not volunteers. This is done in the name of the practice of medicine all of the time; minor changes in the physicians' techniques, or minor medicines, or new uses, or slightly different surgical techniques tried by a physician as part of his practice are research projects in a sense; and it's done sometimes on a patient that has not obviously volunteered for it. And I think that to keep this in mind emphasizes a terrible problem on has in drawing a line as to where anything you're doing is just enough different and new so that you need to go through the procedures of permission and peer review which are required for a research project. Where this new and different thing is just so minor one goes ahead and does it as part of the practice of medicine.

In the Clinical Center we have had traditionally a clear cut distinction between the well and the sick research subject. And about a third of our patients have been well people who are admitted specifically for a research project, or two, or three, in which the investigator needs to study the normal person, both to arrive at some better mechanism or explanation of mechanisms of disease by studying the normal mechanism and then seeing how the diseased patient differs. Or, in the case in which the investigator has some specific

studies in abnormal conditions in some patients and he needs to compare those data with another sick patient. So he studies the normal as a separate category. About a third of our patients are in the category of normal volunteers who are recruited by an office we have for that purpose through various groups on the outside that are largely church groups, but some educational institutions in which the students feel that is is an important experience in their lives to take part in a research project. The other two thirds of our patients are sick and are sent here by practicing physicians who refer them to the NIH for many reasons. A common one that we are not terribly happy about but which we accept and we are glad to help where we can, is when the doctor has tried every known therapy, or every known diagnostic maneuver and finally throws up his hands and says that there is only one place that may help you and that is the National Institutes of Health. That is sometimes a difficult problem for us for several reasons--the patient may not fit in the group of diseases we are studying, and also we may not have a protocol for studying them, or even if we do it is usually not a situation in which we can be dramatically helpful although there are some exceptions. So sometimes patients are referred because there is nothing else that can be done for them. Sometimes they're referred because they have a rare disease which they know we are studying and investigators study rare diseases quite often because they are better able in studying the rare mechanism to understand often the more common one; and then sometimes patients are referred with perfectly common diseases because the doctor has been notified that we are looking for patients with that disease, and we will be glad to take care of the patient during the course of that illness and we are always very careful to emphasize that we will return the patient to his own physician. The care here is free to the patient. So that might be considered a reason why some people are referred. If they have run out of money on the outside, they can still get as good or better care here; but only if they do fit in a stated research protocol. We probably turn down about 60-80% of the sick patients that are referred simply because they don't fit with the protocol which investigators at that moment are looking for.

Now procedures in the past have been slightly different for the protection of the well and the sick patient with regard to the determination of risk/benefit ratios and peer review of what is done for that patient.

With regard to the normal volunteer, the investigator writes up a protocol which is quite detailed, and we can make some available to you if you wish, which is first approved by his boss, his laboratory chief, or his clinical section chief, and then by the Clinical Director of his Institute. Then it is referred to the Clinical Research Committee of the Medical Board, which is a group of investigators from all of the different Institutes, who go over it in great detail, and then they refer it to the Medical Board, which consists of all of the chiefs of all of the services; nine Institutes have clinical services. The Medical Board includes a couple of non-M.D.'s who are on the NIH staff, and an M.D. from the community who has no association with the NIH. The Medical Board then approves or disapproves or approves with qualifications, as did the Clinical Research Committee. The Clinical Research Committee members quite often interview the investigator in person to find out any further details or reassure them about things that may worry them. Dr. Copin had been Chairman of the Clinical Research Committee for a couple of years and can further elaborate on that. The Medical Board may also call upon the investigator if they have something that bothers them. After they approve the protocol, then I go over it and write in my name indicating that I agree or I send it over to Dr. Berliner if I have some question on something that I don't agree with. Dr. Berliner either approves or disapproves according to the complete comments made by the complete Clinical Research Committee, the Medical Board, and me. And only after he has signed it is the research protocol instituted.

The sick patient presents a somewhat different problem, as here we get into the interaction between practice and research. Where the physicians on the ward are taking care of the patient as a patient and where they are doing research is not and has never been clearly indicated all through medical practice and research. Since every patient referred to the NIH understands that he is coming here to partake in clinical research and this is made clear to him not only, hopefully, by his own physician at first, but also by the admitting office and also by the NIH physicians who work him up. This is a slightly different situation from the hospital in which the patient is admitted ostensibly to be treated and then is asked to take part in research for something that he may not have had any idea was being done. So we feel that we have one leg up on the permission process when the patient does enter the Clinical Center because he knows, we hope, that he is coming here for research purposes

and we have him sign that he is willing to leave to be discharged--when the doctor decides that the research project is over. He does not come for the duration of his illness, although we break that sort of custom many many times for professional or compassionate reasons. It is the policy of the Cancer Institute, which has the largest number of sick patients in the hospital to look after their patients continually until they are well or die. Some of the other Institutes do not do this for the very specific reason that they feel that they should not get into the complete practice of medicine. This would limit the number of patients we could get into the study and would limit, therefore, our ability to carry out our mission of doing research in the particular disease area. In those cases the patients are seen for their one initial episode of illness, and it's made very clear to them that they now go back to their family doctor. A complete report is sent to the family doctor, and he can get further advice whenever he needs it. He can refer the patient back to NIH again for consideration for readmission but in most instances we don't promise to readmit that patient through all of his illnesses.

In the case of the sick patient being taken care of by our physicians upstairs, things are not too different from the ordinary university or teaching hospital. The Clinical Associate who has just finished his internship and residency, usually in a teaching hospital, is directly responsible for the patient--the equivalent to the intern in a university hospital. He works up the patients and writes most of the notes and reports to the clinical investigator who has admitted the patient for a specific subject. Protection of the patient and making sure that he receives good care as a sick patient and also good research is the responsibility of everybody down the line from the clinical associate who is the patient advocate throughout to the investigator who may have a little more interest in the investigation. The clinical associates and the investigators work together, one thinking a little more about the patient care and the other thinking a little more about the research; with the chief of the section or branch or Clinical Director being the final person who has ultimate responsibility to be sure that the patient care in exemplary and the research is good. In the past because of the difficulty in determining when a new protocol or when a new project was being started, or when the patient was receiving the kind of routine care that might be necessary for someone with his disease, we did not formally require a written protocol to be approved by a research committee in the case of each decision made with

regard to the handling of each patient. Obviously we can't do this with 350 patients in the hospital, many getting routine patient care. It has been the rules, which you will see, which state that the Clinical Director would determine whether or not something was going to be done for or with a patient, diagnostic or therapeutic. In other words, where the patient is not serving as a normal volunteer, the Clinical Director would decide whether this protocol had to go to committee or not--in this case an Institute committee which looks at all of the research activities going on in that Institute.

We have now changed this in the last year, and the rules now state in Review of Clinical Research Procedures in Patients (this is in contrast to the normal volunteer): Clinical studies that are diagnostic or therapeutic in intent (1) for studies that conform to accepted medical practice the group decision with interaction of the clinical associates, attending physicians, and the service head or branch chief, is sufficient; (2) Studies that deviate from accepted practice will be referred to the Institute Clinical Research Committee which will review the project and recommend approval or disapproval or further review by the Medical Board. (In other words, if the project is particularly critical with regard to the risk/benefit ratio, if it may be considered that the risk or benefit may be more for humanity than for the individual's aid, and it's a sticky problem, then the Clinical Research Committee of the Institute doesn't feel that it can take full responsibility and it is referred to the Medical Board for further review and consideration.) And Section 3 is: Investigative nondiagnostic/nontherapeutic clinical research not motivated wholly toward the patient, where, in effect, the patient serves essentially as a volunteer. All projects involving the utilization of patients for such studies shall be reviewed by the Institute's Clinical Research Committee. This committee can then either recommend approval, disapproval, or further review by the Medical Board. The form in which protocols are presented to the Institute Clinical Research Committees may vary within the Institutes but an appropriate record must be kept of the actions of the committee in its consideration of each project.

Now I should correct what I said before in that this amendment of our rules that are in the gray book, and in a 1966 document from which this was

taken, have been approved by a committee, of which Dr. Wolff is chairman. The Medical Board has not yet given its final approval so that they haven't changed our by-laws yet, but it is the procedure that we are embarking on. The distinct difference is that in the past it has been up to the Clinical Director to make a decision as to how variant from ordinary practice something was, and if it was necessary, even so, for it to go before a special committee. Now he still has to make the decision--the investigator still has to make the decision--as to whether the proposed course conforms with practice on the outside (and that is not an easy decision to make all of the time). But once that decision is made, then it is automatic whether it goes to the committee or not. That pretty well summarizes the procedures in the Clinical Center.

With regard to the controlled clinical trials on the outside which are now a part of the intramural program, these actually go through the same general procedure as for grants, in that the protocol, the application, has got to be approved by the institution which is doing the work; by their own Clinical Research Committee, whose make-up has already been approved by Dr. Chalkley's office. After that, when the application comes in, it is referred through our intramural program, the Clinical Director, the Clinical Research Committee of the Institute, and then to the Medical Board if it involves volunteers, and not to the Medical Board if it doesn't involve volunteers. So that we have a dual check on the clinical studies that are supported by contract.

Dr. Berliner has arrived while I was talking. Dr. Berliner is Director of Intramural Research as well as Deputy Director of Science for NIH, and Dr. Leventhal is his assistant. They are really the responsible people. Shelley do you have any comments?

DR. WOLFF:

I think that you have covered it all very well. I would just want to add that even with a volunteer the Institute's Clinical Research Committee can be invoked to go over those also. And in some Institutes they even require that an Institute Clinical Research Committee report go to the NIH Clinical Research Committee also. So here is another level of checks. I think that you have covered it very well.

DR CHALMERS:

Irv?

DR. COPIN:

I think that you have covered it well. All nondiagnostic/nontherapeutic procedures go through the Clinical Research Committee whether or not volunteers are involved.

DR. :

It seems to me that a clinical question enters into this rather fine scheme, and how that decision is made is critical. Who decides whether it is nondiagnostic or nontherapeutic, or whether it is research enough or innovative enough to warrant putting through the system?

DR. CHALMERS:

This is decided at what we might call the bedside of the patient. By the system of clinical rounds in the Institutes in which the staff physician who brought the patient in describes what he's doing, and the Clinical Director as his supervisor verbally approves or disapproves his decision about which courses to take. There is no committee or peer decision of whether a thing goes to a committee or not; and we assume that in the course of normal patient care that with several people being involved that there is a sort of a peer review mechanism at the bedside. Nobody admits a patient, works them up, studies them, treats them, and discharges them, without somebody else being involved. I think that that is the only thing that we can rely on as a brake or a mechanism of picking up where things may not be following the general standards that we would like them to. Now I beg your pardon, we do have another way; and that is through the head nurse. At the weekly meeting last week, the Chief Nurse of the Clinical Center, said that he nurses had told her that on one of the wards, they thought that patients were being studied, investigated, too extensively before the protocol appeared; and they protested to the doctors that they really thought there ought to be a protocol within this period; and the doctors said that we are getting a protocol together and we have to do these few little things to see how to better write it. Well, the net result of this I think is that the protocol will come forward sooner. So we should put on the side of the patient advocate, not only the clinical associates,

but also the nurses, the social workers, the dieticians; in all of whom we try to instill the spirit of the patient's safety coming first and hope that they as part of the team will instill this in the back room doctors.

DR. BACKUS:

A question concerning indoctrination of the local professional staff when they come to NIH since you do have quite a turn-over here among the professional staff; and also the nursing personnel and so forth--is there a formal indoctrination of these policies?

DR. CHALMERS:

It varies. Recently, about two years ago, or three or four years ago, I guess, the concept of having all of the clinical associates together for a formal indoctrination was dropped because it was so apparent that if you asked them, even though they were the brightest young doctors in the country, if you asked them a week later what they learned that day of indoctrination they couldn't tell you. I think this is true of all new functions, so to speak. When you get everybody together and you tell them how they have got to do things it goes in one ear and out the other. So we have stopped having meetings, and what we rely on now is the man who precedes teaching to one who follows, the repeated rounds and conferences and conversations, with regard to the doctors. With regard to the nurses, they have an extensive 2 to 3 month rotation among the various Institutes, among the various wards, and attending various sessions before they are called to nurse here and really start functioning. Presumably they are going to be here longer. Our clinical associates although they come for two years, are only on the wards for one. Then their second year is in the laboratory; during that time they may supervise the ones on the wards. During the transition period, they are responsible for training them. Most of the clinical associates come, however, from teaching hospitals that have had active clinical research programs so that they pretty much know what is going on.

MR. BROWN:

I think that I now have some understanding of the review process for new studies. I would be interested to know though how the process works when the study is in progress and some of these factors that influence your

determination of risk and benefit change either because someone else is doing a study, or some new information comes to light.

DR. CHALMERS:

This is one of those things that we all feel uneasy about because it is hard to tell just how rigid to be about re-review because of the workload. We do have a rule that a protocol that is approved at a certain time has got to come up for review again, both by the Institute and by the Medical Board. That review--Shelley maybe you can describe it because I am not sure about the timing now, since it was changed.

DR. WOLFF:

The whole study must be resubmitted to the Medical Board at least every six years with a detailed analysis of the expected raction that occurred and new information. We also re-review every three years. Many of the protocols now contain restrictions regarding how many people can participate or how long the duration of study might be. If I say that I am going to study ten people for three years, at the end of the three years the study is over whether I am done or not. You are supposed to report any unreported reactions at that time. Some protocols are requested by the Clinical Research Committee to have a re-review more often than every three years. In one Institute a malaria project protocol was resubmitted at the end of the second year. They had to report to the Clinical Research Committee the details of what had happened during the previous year. But there is an absolute requirement that all protocols must be resubmitted and reconsidered by the Clinical Research Committee every six years.

DR. KATZ:

Do you have a regulation that if there is a reaction not anticipated in the protocol that it has to be immediately re-reviewed?

DR. WOLFF:

I don't think that there is a specific regulation on that point, except when it is involving a new drug. That is required by the drug laws.

DR. KATZ:

Would you want something like that?

DR. WOLFF:

In general, this is reported, but I don't think that there is a specific regulation that says we must.

DR. [illegible]:

In the protocol, there is a section which is entitled "Hazards and Precautions". As soon as there is any information that is sufficient to alter that; the investigator has to make this known to his Clinical Director, who then makes the decision as to whether or not the whole protocol has to be re-reviewed or not in the light of this new information. Also if there is any untoward effect of a procedure, expected or otherwise, we expect to find this out from the investigator. The problem in all of this is that I think that the integrity of the investigator is the key, regardless of the review procedures or anything else, because we're dependent upon the investigator to tell us what he is going to do to evaluate this, and are dependent upon him to do exactly what he said he was going to do. If the base level we approve is up to a certain level and he feels he would like to go further, we have already told him that he can't. We don't really have a check on him, to know that he is not going to go haywire. We're dependent on his integrity as an investigator, as a scientist, as a physician, not to exceed the limits set. The only--I think this is true in practice as well--the patient goes to the doctor, he makes the assumption that the doctor knows the best possible thing for him--I don't know of a useful way of getting around this. I can't think that we have to have someone checking on every drug that goes in, but a nurse presumably is there, and knows what the protocol should be, and this is the only check that we really have at the bedside.

DR. KATZ:

No, but the integrity of the investigator doesn't really help, because people don't really know exactly what they ought to do. Like, for example, Dr. Chalmer's example earlier of the nurses reporting that some studies were done before the protocol had been submitted. There ought to be a regulation that this should not be done.

SIMULTANEOUS DISCUSSION:

There is a regulation.

DR. CHALMERS:

Well, there is. The problem is, what is the study that's being done? Is it part of routine work-up of the patient, or not--and the definition. This was a difference in the nurses idea as to whether this was a research thing that was being done; and then the doctor said that this was just a routine work-up.

DR. KATZ:

Exactly. But you have been working this area at the firing line; I've been working this area in the ivory tower, and I really don't know how to make these distinctions. As your most recent regulations so nicely indicate--that you finally felt that you really needed to narrow the gap here, because it really was so difficult to make the decision as to what is diagnostic and what is therapeutic and what is experimental. But I think that there are a few things that one might really set out and tell people--that if they violate these kinds of rules, then they do this at their peril.

DR. [illegible]:

Oh they know that. That is clearly not only stated, but implied. The perils--for example the checks and balances of these in our services--the roungs that we have are not just rounds by the investigator; I round every friday afternoon with upwards to twenty physicians; and each patient is gone into in detail. Many of these physicians have no personal interest in this particular group of patients; and discussions of this sort are carried on in addition to the regulations we have. But I have to agree with Dr. Copin if somebody wants to do something; then we can't regulate that.

DR. [illegible]:

Well, there are mechanisms for an investigator to request a raise in dosage for instance, for a drug. There are ways for him to do this. For example, if the Medical Board and Directors have approved a given dosage of a drug, up to a certain level, and he finds that this drug is not having the effect that he expected--in fact the information comes back that this is a very harmless dose--other doeses have been published that are higher than this--he may then ask for interim approval to give a higher dose. He has a patient now in a situation where the dose is appropriate to be increased. It

isn't appropriate to wait for this whole review process. He can then pick up the telephone, and telephone the Chairman of the Medical Board, the Chairman of the Clinical Research Committee and obtain from him an interim approval for one patient or two patients to go beyond this level. So there is no excuse for him to have to use subterfuge or do anything else. There are ways to get the job done through appropriate mechanisms, if these are appropriate and proper to do it. So he isn't bound in this way. And I think most investigators know this because I know by the frequency of calls that we get. Now sometimes we will approve it and sometimes we will disapprove. Now this is up to our own judgment and caution, and we may seek advice of other people in this. It is not a five minute emergency, it is usually one day or two days as opposed to two weeks or a month. So that there are methods of getting around this and the mechanisms are used.

DR. HILTNER:

Who is the "we" when you say "we"? Is that the research committee?

DR. :

Yes, the Clinical Research Committee

DR. HILTNER:

The Clinical Research Committee?

DR. :

That's the Clinical Research Committee, (it) meets every other week; and the Medical Board meets every other week as well. The Clinical Research Committee meets the Wednesday before the Tuesday that the Medical Board meets. Then it has to go to the Clinical Director. This whole process can take up to three weeks to a month. If an investigator has a relatively minor change in his protocol, or he wants to institute a protocol which does not appear to have any risk and has a good deal of potential benefit, and if it appears clear that it will go through the various review procedures, the Chairman of the Clinical Research Committee and the Chairman of the Medical Board together; they give interim approval for this protocol. But this is only usually for a limited number of patients, for a specific circumstance which may not amount to exactly an emergency, but with sufficient reason to alter the usual procedure; and that is done as an exception. Although I think we get many more requests

for this than are actually carried out.

DR. HILTNER:

Could I pursue another aspect of this same question with Dr. Chalmers? And that has to do with the Medical Board, to which you earlier referred, if I understood your earlier remarks. This is made up of physicians here, heads of various Institutes plus a couple of physicians from outside--that is, who are not physician members of the Institute.

DR. CHALMERS:

There is currently one physician from the outside who was put upon us as a consultant because it gets him a parking space, but before that he had no connection.

DR. HILTNER:

But if I am understanding, this is what I'm asking, all the Medical Board, I assume in a sense, is the final authority about these decisions.

DR. CHALMERS:

Well, I sort of act as an intermediary in sending it on to Dr. Berliner. And Dr. Berliner is the final authority. He reads through their recommendations. It's his signature that really officially approves. And I should add also that the Medical Board has other people on it who are elected each year, and rotate off and on. So we do have somebody from this.

DR. HILTNER:

Well, what I am really trying to get at--since many of the issues that are involved are not purely medical in an historical sense, and seeing this is a National Institutes of Health, not national institutes of medicine, whether anybody but physicians have anything to say about these decisions. That's the thrust of my questions.

DR. CHALMERS: Well, we currently have two people who are not physicians: one of our more senior social workers, and then a lady from management part of the NIH who is socially conscious and always interested in this aspect of things.

DR. :

Plus we have a dentist, and two lawyers who are ex-officio members. They come, they're not really members, but they come to advise us. So there are five non-physicians.

DR. KATZ:

These are NIH lawyers?

DR. :

They're from the. . .

MR. MANGEL:

Yes, but they aren't any part of the Board.

DR. CHALKLEY:

They aren't paid by NIH either.

DR. :

NIH has no lawyers.

MR. MANGEL:

We disown the Board.

(Laughter)

(SIMULTANEOUS DISCUSSION)

DR. :

So there are fifteen members of the Board; seventeen including the two non-members, of which almost a third are not physicians.

DR. CHALMERS:

But this is a recent change. It used to be purely physicians.

DR. BUTLER:

I would like to ask another question--grievance questions. (1) When you refer to the integrity of the researcher, who in the final analysis is

held ultimately responsible if (1) the research does not prove out as anticipated in scientific value, in terms of the quality of the research, and (2) if the risk is determined to be too high for the participant (the subject) whether they are volunteers or not; and in case of a suit regarding the non-value of this; who is the agency of final responsibility when something is being done intramurally?

DR. CHALMERS:

Well, I guess Dr. Marston, the Director of NIH, then Dr. Berliner, then there is the Institute Director, Scientific Director, and Clinical Director, and of those three, the only one who really knows the details would be the Clinical Director. And down that chain of responsibility to the staff physician, the clinical associate, and the patient. And then the other half of the split is to me in my office and then down my chain of responsibility which is through the nursing services, dietetics, or through our indirect influence on the physicians, which is effective through my job.

DR. BUTLER:

There is no direct influence on the physician--if he says "I am going to pursue this anyway," if he thinks he's on to something.

DR. CHALMERS:

Well, his Clinical Director will stop him, or his Scientific Director or Institute Director--that channel is a direct influence.

DR. BUTLER:

Could you give us some illustrations of the types of researches that you would consider either not approving or, if started, of stopping?

(SIMULTANEOUS DISCUSSION)

DR. :

Some proposed uses of normal volunteers have been turned down by the research committee.

DR. BUTLER:

On what basis?

DR. :

On the grounds that the potential risks outweighed the potential benefits.

DR. :

We recently turned down a project where they wanted to bring in patients and pay them a fee for coming in to be studied, not here, but in another institution, and we felt that this was undue coercion, and that's been turned down. There have been a number of things; liver biopsies have been turned down in the past.

DR. BUTLER:

There are some cases that really go beyond risk, because there is either reasonable or absolute certainty of death or absolute certainty of great harm to the participants; and yet there is research going on in this area. For example, where people are near death, or one of the more dramatic that I consider the relationship between consent, informed or uninformed, and heart transplantation, when they call a heart transplant donor a volunteer. I happened to hear Dr. Cooley on television with the wife of one of his patients, make a request for a heart transplant donor. And I thought this was--now this is outside of your risk chart.

(SIMULTANEOUS DISCUSSION)

DR. CHALKLEY:

Do you remember what she did a year and a half later? She sued Cooley for three million.

DR. BUTLER:

Yes. This leads to one other question. I would like to ask your feelings about two things. (1) Are your guidelines undergirded by any legislation? I know that a lot of legislation is being proposed, but is there any present legislation undergirding the guidelines? So that should there be a clear case of violation, or something, and you try to enforce it, and it goes to court, and it is determine that there is no law.

DR. :

Except for when it concerns new drugs; and then they are under the guidelines of the FDA.

(SIMULTANEOUS DISCUSSION)

DR. BUTLER:

But then there are no general regulations in the areas in which we are concerned? The second question on that point is what are your feelings about the possibility of a commission on the use of humans in research--a regulatory commission such as the FDA. Anybody's feeling--I would just like to know what the feeling is.

DR. :

My initial reaction is I would be very unhappy to see a new governing agency formed since the past performance of governing agencies has left something to be desired. I think that there should be regulations, and there should be some way to enforce them, but I don't think that establishing a new agency is necessarily the answer.

DR. BUTLER:

Does anyone else have any. . .

DR. :

I would agree very strongly with what he had to say. I think that--I don't think that a regulatory agency of any sort would add anything to the current regulations, or regulations as amended, as we will amend them, where we will make them more specific in certain areas. I don't know what additional input a commission would have into this.

DR. BUTLER:

Well, they would provide the law on this subject. It would necessarily carry with it some type of implementing or some type of form or structure where the responsibility would be based in the agency or elsewhere for it. Now, for its implementation.

DR. CHALMERS:

I would like to answer your first question a little bit further, where you talk about the things in which the risk is definite and more than definite. We don't want to have anything to do with that business--we, the people who are doing research in the Clinical Center and the prople we are responsible for. If you are going to do research in humans you have to be a physician first. And if you are going to be a physician first, you have to really take clear cut responsibility for the welfare of your patient. It is hard to conceive of a situation in which you would make a decision in which the risk was definite without benefit that was more definite. And I think that one does that once in a while when you take out a whole stomach in the effort to cure the patient's cancer and with a 20% mortality, whereas just taking out half the stomach it would be 5%. You're taking a big risk then for what you think--you assume--would be greater benefit. But conversely, I think we have to work in a milieu, in which, we as physicians, in which we instill in our physicians constantly, the fact that if a patient comes to them for care, whether it be a research hospital or not, their primary responsibility is the safety and welfare of that patient.

DR. KATZ:

Dr. Chalmers, I was just going to talk about that. You are actually in a very enviable position here; that this is a research center, that most of the people who come here know that they are coming to research institutions-- So you are not in the same kind of dilemma as investigators are in other medical centers, where the differences are often unclear. And all of you are interested in advance in knowlege. So shouldn't you under appropriate circumstances be able to step a little bit out of the physician role and be more the investigator. I'm trying to talk about this very carefully because to be sure, an investigator can still be a human being, but an investigator can be a different human being than a therapeutic physician human being in the actions, because he has also different kinds of intents and goals. I am not really referring to informed consent, whatever that means, but if you have a group of intelligent patients, whom you are doing research on, and you want to investigate something that has somewhat greater risk that go sort of in your box, you know. Don't you feel much more comfortable if you can discuss it with them, and talk it over with them; they are willing to participate.

To really go a little bit further in order to get to the thoughts that you would like to get then if you were dealing with a group of patients who cannot comprehend, whom you cannot make your associations with, etc. But in your role as an investigator have you got a similar role to that of a therapeutic physician and doesn't consent to become a part of this box too?

DR. CHALMERS:

What I think you're implying, and I believe this very strongly, is that in the ordinary doctor/patient relationship where research is not initially involved, the patient is a real captive then in research that develops, more I think than under any other circumstances. Because the patient has come to the doctor and said "get me well" and he is not going to antagonize the doctor, or he does so at risk to his health. So that, what I guess you're saying, is that here at NIH that situation does not quite hold. The patient comes and says do research on me and I hope that you will get me well in the process. It's true, but I think that you have to really be trying constantly to hold that line of really doing what's right for the individual patient first, taking minor risks for general knowlege, and hoping that a series of minor risks will result in a major benefit to mankind. But that you won't be forced into a situation where you have to take a major risk to the individual's life for the benefit of mankind.

DR. KATZ:

And with the understanding patients, would you be willing to take somewhat greater risk, or not; would that not make any difference to you?

DR. CHALMERS:

Oh, I suppose, maybe a little bit, in the fact that they are here and understanding might make some difference. That at least you are not deluding them into thinking that your primary function is their care.

DR. [illegible]?:

As far as the committees go, I think that we're more careful about that. I can give you some examples. There was a psychologist who was interested in performing some tests on normal individuals, and wanted to approach some of the parents of children who had leukemia. He was on the same floor, and he could see them sitting out in the hallway. He asked if it would be possible for him

to go ahead and ask these parents to participate. The Clinical Research Committee turned this down on the basis of the fact that they felt that there was the possibility that these people would feel undue coercion to participate. But this was a minor procedure, the benefits of which were questionable. And the risks were absolutely negligible in terms of the individual, but in terms of their relationship to the institution they would feel that because their child was on the ward receiving care that there was some implicit coercion in this, in their being chosen, and being asked to come in. We felt the investigator could just as easily obtain other subjects who were under different--or not under the same sorts of stress. And this was an example, I think that we were sort of protecting the institution from thoughts that anyone who happens to be visiting can be grabbed off and used as a research subject; and in this case a psychological test which was minor. But in other cases perhaps more substantial and a risk. At least that could be the interpretation of the parent; and for this reason we turned away from using this population and suggested that he go elsewhere and/or that he speak to the physician in charge to find out whether or not it was appropriate to approach these people. But we would not give blanket approval for this, and I think this was leaning over backwards to avoid a situation of undue coercion. We're very much aware of this problem, and we're concerned about it. We're concerned about the image the institution gives to the various people that become patients, or relatives of the patients here.

DR. :

May I just add to that. I think that in some of the conversation when I was talking in the singular about whether this individual could feel that--I think that the system of checks and balances has been developed here even though it may not sound as though it has. It doesn't allow for that individual, unless he is a man without integrity and wants to go on and do something--it does not allow him that kind of privilege. I think that he has a series of steps to go through that prevents that sort of thing.

DR. BUTLER:

Are any studies being done either in NIH inclusive of NIMH or sponsored, or at least approved for funding where suicide is involved--in studies of suicides? If such studies are funded or if there is a center for such study--how are these studies designed? What would constitute, for example, a control?

DR. :

I don't think that any of us can answer that question. There is nothing here at NIH involved in this, and if there are any such studies they are in the Institute of Mental Health.

DR. BUTLER:

The reason that I asked this is that just as Dr. Hiltner is concerned, I'm concerned beyond what is knowledgable in medicine, because some of the greatest abuses are presently taking place among--well, I don't want to single out a profession--but, if a psychiatrist is doing a study there is a certain kind of rigidity that is expected of him; if a psychologist is doing a study, or a teacher of psychology is doing a study with us, he is actually running the risk of altering behavior that he cannot control or doing some damage. I started out in 1964 calling this the Timothy Leary syndrom because certain things were given great dignity simply because they were done by both psychologists or. . .

DR. CHALKLEY:

. . .and a Harvard one to boot.

DR. BUTLER:

I know. Right. But the points are these; the need for some sense beyond just the code of ethics or just a code. I also wanted to ask some questions about the relationship between a philosophical theory which is at one level (and you can put some of the early theories of medicine and therefore the theories of society in this category) from a moral code, which is one step closer. It is reflected in such things as the AMA Code of Ethics or in this instance the Helsinki or Nuremburg Codes. But if those are the only things which are there, it then becomes a matter of pure discretion or pure integrity in the manner of whether a society can have certain protections and there is underlining this the serious question of when do these things become a matter of necessity to sanction or to support them by a body of law; and whether we are at this kind of point in respect to a number of things which are going on. I would also just like to kind of sharpen that--ask if there are any studies presently engaged or supported which have a kind of longitudinal character; the projected studies of the natural course of the disease entity as was the case with the Tuskegee Study. The Tuskegee Study evolved into that,

it did not start as that; it started as a treatment demonstration. But this thing that we are now concerned about evolved as a dimension of that, in order to determine the natural course now. There are some things that develop into certain--I remember a remark from the University of North Carolina Hospital when a nurse, and this is something that I happened to witness, enquired about the treatment of a patient. And this particular researcher was interested in the condition that was to come about. He was not interested in the present condition of the patient. And I am sure that he did not intend it in the way that it came out, but he said in effect "I am interested in the condition that is about to take place, so let it happen." You treat the patient and prevent the thing in which he is interested. And these things do happen. And if we do not have enough patients for a certain advance condition, there is a question of whether you stop and treat patients. And there is a question of whether the patient--and I ask a question of the concept of consent and I think that the concept of consent would raise a lot of conditions beyond just the simple factor of volunteerism.

DR. [illegible]:

May I take some exception to what you just said?

DR. BUTLER:

I am just putting something before you.

DR. [illegible]:

If you imply by the example you gave by the physician at the University of North Carolina, that he was allowing something deleterious to happen to that patient.

DR. BUTLER:

I don't mean to make any inferences. I'm just trying to expose--enter some evidence where there are concerns--my real concern is whether this kind of committee in the present atmosphere--whether we should suggest or not suggest that there is a need for undergirding the present guidelines, and undergirding the various codes that we presently have and the AMA. As even in the days way back in the 30's there was a committee on ethics which approved this whole process which developed, and it was a county/state committee. But they did have a committee on it so they did not consider. . .

DR. [redacted]:

Well, I can't say what happened in the 30's. I can only tell you that in the last 12-13 years in this institution, things have changed considerably. And I think much more so than one would have predicted 12 to 13 years ago. We did things that no one would dare consider doing today and I think--I don't know of any physicians in this institution that would allow something to happen that might be deleterious to the patient.

DR. BUTLER:

I'm not saying that this would happen--because as I was saying this was almost, well about 8 years ago. It was in '65 I think.

DR. HILTNER:

Well, how do you account for the--now what should I call it--the change in ethos or decision mode of making decisions, or whatnot that produced the alteration to which to make reference?

DR. [redacted]:

I think that there are many things that go into it. I can't explain it too simply. I think our ability to do things to patients had increased enormously in the category--the advances that we have made in medicine has allowed us to do things that we never were able to do before.

DR. HILTNER:

And with less potential harm?

DR. [redacted]:

Yes, sometimes.

DR. CHALKLEY:

Or maybe more potential harm and that is why we need more controls.

DR. [redacted]:

Yes. I think also the concern for social reactions has increased enormously in the last three decades compared to the century. . .

DR. HILTNER:

What I'm trying to find out, you see, is whether the technology that is produced is for a higher ethical sense.

DR. [redacted]:

I think it is minor, because, I think back in the 40's and 50's it was not the general practice to obtain informed consent for the ethics. It just wasn't done--whatever the reasons may be, and I think that I guess that maybe more consideration of what was going on has led to these practices. But I think that there is no question that it is different. I think that the Helsinki Declaration had something to do with it.

DR. HILTNER:

Part of what is involved is that the public got interested in drugs and so it had some right to have been represented in the way in which new drugs were used and so on. In general, as this increased, when it comes to the Federal drug thing or otherwise, has this impeded the work of NIH or made no difference?

DR. [redacted]:

I don't think that this has made any difference. Let me say that some of the people who are dealing with new drugs, feel that it makes a big difference.

DR. HILTNER:

You mean they think that it is better?

DR. [redacted]:

No.

DR. HILTNER:

Worse?

DR. [redacted]:

No, they feel that you can't study drugs in the United States any more.

DR. HILTNER:

The drug regulations have been too rigid and strict? You mean today the regulations have been made too stringent and narrow?

DR. :

Yes, that's right. That is a common opinion and you talk to people in the pharmaceutical industry and those people who have done much of the trials; they can't do it in the United States anymore, they have to do it some place else.

DR. KATZ:

Are there investigations you would like to do and that you feel you cannot do because of the guideline constraints that exist at the moment. I'm not talking about what you would not do for personal reasons--but what you would be willing to perform but you feel that would require informed consent--whatever that is--and HEW guidelines would impede your doing it or you are concerned about a lawsuit.

(SIMULTANEOUS DISCUSSION)

DR. :

I think that there are many studies that individuals would like to do which when considered by a group it is thought better that they not be done. In other words, the enthusiasm of the individual for the project may put much more on the benefit side than his colleagues would put, and he would put less risk than his colleagues would do, and therefore I think that there are many projects that an individual would like to do which will not get by a group of his colleagues simply because they weigh the values.

DR. KATZ:

That's not precisely the question I'm asking. I have something very specific in mind. Are there within your group people for instance who would like to do research projects that they feel they are precluded from doing because of the climate of external restraints that exist at present?

DR. :

As I was going to say. It is difficult to differentiate now in 1972, external from internal. There are questions which I would like to see answered, but would not ever suggest that they be answered because I would consider them to be unethical. I don't know whether we would have done it 20 years ago or not in my own research. I think the question that people would ask, which is

a legitimate one, they would ask about constraints now, is that there are a number of things that we use every day and do every day--that if they were discovered today, that they would never come to be. For example, cardiac catherization. I don't think that today to propose cardiac catherization on normal volunteers for the first time would get through our medical board.

DR. KATZ:

That's whats wrong, you see, that's whats wrong with our present guidelines. Because in many ways they are much too restraining. What I have in mind is one of my colleagues at Yale would like to--has a very good research project--he wants to mate human beings with higher apes--for very important scientific reasons. But he doesn't know where to go to get approval.

DR. :

He wants to do what?

DR. KATZ:

Mate human beings and the higher apes; he's a specialist in interspecies hybridization.

DR. :

He wants to inseminate higher apes. . .

DR. KATZ:

Both ways--he has to eventually do it both ways.

DR. CHALKLEY:

Any ideas?

(LAUGHTER)

DR. KATZ:

Yes, of course--he can--of course all of these things are possible. But you know it creates all kinds of interesting problems, because in a sense we really have no structure where these things can be discussed, debated, and figured out now. And I was wondering if you have similar kinds of problems?

DR. [redacted]:

My kinds of problems are miniscule compared. . .

(LAUGHTER)

DR. BUTLER:

Is there a possibility of developing a forum for such determination, in which it would be seriously entertained? There seems to be something between the direct involvement of the human being and an exploration. Now, most of the medical schools are developing some kind of structure like a committee of advocates, or a committee on research which they hope will be such a forum. The question is whether you can move the value structure within the mores because we are going to have to begin to accept some things which we have clearly rejected as being unethical. One of the questions that came up in the context of our reading was this matter of whether this would be justified, and I have the distinct impression that when he said "justified" he did not mean the same thing that you would mean, when you just say now whether this would be justified. You know, this kind of undertaking. I don't think that the consideration about volunteerism and informed consent had even evolved in the context. But there was something that you can call quasi-ethical or quasi-moral in the use of the term justified rather than whether it be approved, or whether it be funded, or something of that sort, because even there it was clear that the government could not fund it and they went to private sources to try to get funding so that was not the question in the concept of whether it was justified. Whether it was socially justifiable or some other. I'm trying to settle on some of the. . .

DR. [redacted]:

I don't know whether everyone would agree with me, but most of the research that we would consider unethical; most of it has not been very good research. Most of the results that have come out of such research has had very little lasting value.

DR. CHALMERS:

This leads me to the point that I was going to make--I think a major factor in determining the change in ethics in the last ten to twenty years, has been the experience with and the realization that clinical research can

be done well, can be scientific, and that when it is, it is really more ethical than the kind of clinical research that was being done in the past. As an illustration of that, your question about do we know of any other long term studies. The best example I know of is the exploration of the oral anti-diabetic or hypoglycemic drugs in patients with diabetes in which soon after the drugs were introduced, a group of people asked the question, which is critically important, do these drugs by lowering the blood sugar reduce the requency of cardio vascular disease down towards the level that one finds in people who don't have hypoglycemia. It was a logical question to ask, and 99% of the physicians in the United States embarked on treating everybody on the theory that of course they did. Because if you had a normal blood sugar you would be doing better. And one small group set up a research project which might, I suppose, on some standards be criticized because they withheld the therapy from a group of consenting people with diabetes--they gave them placebos. And they gave some others insulin, which meant they had to inject themselves everyday at great inconvenience; and then they gave two groups oral anti-diabetic agents. The study was conceived in 1957, started around 1960, followed the standards of good control trial, of good clinical research, which became well known during the early 50's in this country. And the patients consented, the protocol was approved, and the study is still going on. And it turned out as you probably heard, that the patients who were deprived of the oral drugs were the lucky ones; and their death rate has been distinctly less than the patients who were assigned the oral drugs at random. The study has not been overly accepted by practicing physicians, because they have been using these drugs for so many years and are convinced that they must be effective. They are reluctant to now call in their patients and now say "hey, those drugs I told you were going to prolong your life have really been shortening it." So that we have the reverse situation which has convinced me of the importance of keeping the practice of medicine in mind at all times when you are talking about regulating research. Really, shouldn't informed consent be required if you insist upon giving an oral hypoglycemic agent when the only research that has been done in the field shows that they shorten life?

DR. CHALKLEY:

The only difficulty that you get is the woman who works right up the hall from us came in the other day and told me that she had been talking to a physician about her blood sugar level, and was it too high? She told me, and

I said yea-gods, yes. She said, "well, maybe I had better go back on my insulin." She had been off for 45 days; she just hated to shoot herself with a needle. I think that she is a candidate for pills in this case.

DR. CHALMERS:

Well, she may be, as long as she recognizes the possibility that it may shorten her life. And that rather than go on a diet or take insulin she would rather take that risk. But right now people are not even required to know about that risk because that's the practice of medicine. And in the practice of medicine you don't have to inform them; you don't have a regulatory body so to speak telling them what they have to do. One point I think that is important with regard to having laws regulating research is that they ought to be considered in the environment of the practice of medicine, because if we are not careful research looks like something that's evil and looks like something that needs to be regulated by law. And in the practice of medicine the doctor is allowed to do anything that he wants to. In my own considered opinion, if I am sick, I want to be a part of a research project. I think I would get better medical care as a research patient as long as the research project is well designed and executed according to the standards which have become fairly well accepted and as long as it is something that is likely to end up with a worthwhile answer; and is not just sort of the casual, irresponsible trying-one-thing-after-another without any possibility of learning whether it helped the patient or anyone else--which is what the practice of medicine often is.

DR. KATZ:

You are so right. When I started working in the area of human experimentation, after a few years it dawned on me, and it very soon dawned on some of my colleagues and then they became annoyed at me again, that the kinds of things you are talking about with respect to experimentation equally applies if not more so with respect to medical practice; and what kind of pandora's box are you opening up now? Because if one thinks this through conceptually one comes exactly to your conclusions. And you know, I was a student of yours when I was in medical school and then I was a student of yours again when you have been writing all of the material on the control trials; and I am very much impressed with what you have written on this subject. But how can we really

begin to make some of these things part of medical practice? Is there any way of institutionalizing this, of regulating this, so that we won't get any outside regulations? Because the danger is great if we don't begin to police ourselves that we will be more and more regulated by governmental agencies.

DR. BUTLER:

I think Dr. Katz has pointed to probably the most difficult aspect of the total work of this committee. And that is to try to prevent an emotional onsleught that will bring about a product that is worse than the situation that we presently have. But at the same time making address to what is felt to be in--well, even among rational people--the pattern of activity that may just engage--for example, in cancer research and certain other patterns, where they're just on the brink of a break-through, like anything else, there is a point at which the researcher is so close to this thing, that I just intuitively feel--and I know that it is going to cost--but this is the same thing that a general says when he asks for volunteers, you know, that's why you have suicide squads in various branches of the military, or you do certain kinds of research in the military which is under specific edicts and not for the benefit of participants, and not for the benefit of anything in their immediate society except the--increase the sophistication of the military concern--whatever the concern is at that point.

DR. CHALMERS:

Let me just answer Dr. Katz: I think that there is a way out, and I think that that way is proper education of physicians so that they learn to examine data and act on the data instead of on the latest company advertising or on inadequate research. And if they can appreciate what good research is, what good clinical research is, and draw their conclusions from weighing the conflicting good clinical research, they may make some step in the right direction.

(SIMULTANEOUS DISCUSSION)

DR. BACKUS:

May I just say, Dr. Chalmers gave us some of the reprints that Dr. Katz alluded to. We were unable to get them to the Panel members in time for this meeting. We will send them to you a little bit later.

DR. BUTLER:

Are there any instances of inner-NIH approved research in which a disease entity is introduced into a control, who is a normal person, when you are studying for example, something relating to sick patients, and you need well patients as controls for the purpose of making a determination as to what difference may occur between a sick person and a well person? Are you supporting--do you know of any instance in which you are supporting such a study in which they actually introduce a drug, for example a cancer. . .?

DR. [illegible]:

There are studies involving the production of respiratory infections, common colds, in order to test vaccines. For many years there have been studies in malaria, in which normal volunteers have been innoculated with malaria.

DR. BUTLER:

I was kind of intrigued. One of the reasons I asked the question was that in this same historical milieu, there was a theory that a fever had some kind of beneficial effect in subsiding and even curing syphilis.

DR. CHALMERS:

Oh yes. Dr. Berliner and I worked in that during World War II.

DR. BUTLER:

And the introduction of malaria was one of the suggestions at that time.

DR. BERLINER:

That was the accepted practice for the treatment of syphilitics at that time until penicillin.

DR. BACKUS:

Could I ask a question that was--going back to some previous discussion--in your clinical rounds, is every patient here seen at one time or another during clinical rounds?

DR. CHALMERS:

I think that this depends on the Institute. Shelley sees every one of his. In some Institutes the Clinical Director doesn't see every one because he doesn't get around that often. The patient may come in on a Monday and go out on a Thursday, or something, and he might miss him. But the Branch Chief would see him in that case.

DR. BACKUS:

The question I was getting at was whether this doesn't consitute another kind of input into the question of whether more than one person sees. . .

DR. CHALMERS:

We think it is, and we think that if it is done in the milieu of good medical practice, he is taking good care of this patient or this volunteer. It is a protection for the patient.

DR. CHALKLEY:

If you have a death on the service, how many of these go to pathology rounds or clinical pathological conferences?

DR. CHALMERS:

Our autopsy rate is about 90%, and report goes out, and then again the Institutes have various ways of discussing these. The Cancer Institute has the largest--they probably have 90% of our deaths--sends out a monthly bulletin which describes not only the deaths and what they died of, but also any other untoward events that happened.

DR. BACKUS:

Are there any great differences in the way the different Institutes carry on these functions, or are they pretty uniform in for instance the reports on autopsy?

DR. CHALMERS:

Well, they vary because they are individualized, and some of the Institutes never have a death so they don't have a formal structure for the review of deaths because it is so rare. Whereas, Cancer Institute would be different. Surgeons have a different method of looking at their bad effects than an internist.

DR. BACKUS:

I guess what I am getting at is really a broader question. Is there a general kind of interest and concern about what is going on, and isn't that effective in a way that a number of people know what is going on at a time? Is you review here, the formal is one aspect, of what one might call the continuing process of knowing what is going on in the Clinical Center? Now, many institutions around the country, especially before we set up the assurance mechanism, we were told that in many instances, the administrators at least, and many of the other people in the institution, knew nothing about what was going on in research--in the research activities of their clinical program. Things were kept pretty quiet. We saw more of what was going on at NIH through the grants mechanism than they saw locally at their own institutions, but I get the feeling that that might not prevail under these circumstances. I'm just trying to get a feel for that. Is it hard to keep a secret in other words?

DR. CHALMERS:

Well, everybody eats in the same dining room. I think one other control mechanism which we didn't talk about is an extensive system of inter-Institute consultations. If a patient is on a research protocol in Institute A and he develops a fever of unknown origin. Well, then, one of Shelley Wolff's people will go down to see him. In the course of investigating that fever he will find out what kind of research is going on and if he disapproves of it he probably makes some comments about it.

DR. KATZ: Has it ever happened?

DR. CHALMERS:

That they disapprove, and make comments? Well, it's hard to tell because they don't get into very formal channels. It's more verbal.

DR. KATZ:

You couldn't give me any examples of formal complaints, could you?

DR. WOLFF:

No I don't think many. But I have complained.

DR. KATZ:

Formally? In writing?

DR. WOLFF:

No. Not in writing, but I have gone to see the people.

DR. CHALMERS:

We have to be careful that they don't stop sending consults.

DR. BACKUS:

Well, what are you missing? The things you pick up are one thing, but what about everything that you don't see.

DR. WOLFF:

I don't want to sound naive or modest, but I don't think that we are missing too much in this institution. I think this is a unique institution, and when I go out to other places I see--patients are being admitted here for research, this is our business--and I think that we should do it better than anyone else, and I also think that we should set the example. I think that, without sounding terribly chauvinistic, I think that we do a very good job of it.

DR. [illegible]:

I think that it is very important to remember, that not only is the patient admitted to do research, but the doctors work here to do research. So that their entire professional career, the evaluation of their accomplishments, and a whole variety of things that relate to promotions and the quality of their work, and its evaluation and so on, is dependent upon the judgment of their peers. And I think that the thing that does not happen, can't really happen, in the mechanism is that an individual admits patient to the hospital does something covert, sort of hidden away in the corner, and discharges the patient, in the direct individual personal relationship that might be more typical of a private patient relationship in a private hospital. The opportunity to admit a patient to this hospital is a rare privilege that I think people accept and appreciate as the purpose they're here.

DR. BACKUS:

That raises another question, that came to mind a little while ago. Do you have enough research to absorb all of your resources and more than enough opportunities to do what you would consider important research without having to go to a lot of extra effort to find things to do?

DR. CHALMERS:

We have no shortage of problems.

DR. BACKUS:

I would assume this to be true, especially being the big institution you are. You probably have many more opportunities for pursuing things and with that selection you can probably, under those conditions, avoid a lot of the problems you might get into otherwise.

DR. [redacted]:

There is one other factor that I don't think has been stressed here enough. And even though these young men work for us and we may feel they are intimidated by that fact that they work for us, the group of clinical associates that comes through here are really the cream of the medical crop each year. And these are basically very bright and honest young men. I have never met one yet who hesitated to say something when he felt we were doing something wrong. And there are 200 or so of them pumped into this institution every year, and leave at the end of 2 years or 3 years. They are probably one of the better checks and balances. I've never found one afraid to come to my office and tell me he thought we were doing something wrong.

DR. BACKUS:

Do you think that you are serving as a training round for ethical research that is going on outside of NIH?

DR. :

Unquestionably.

DR. KATZ:

But you know, all of the students really know what is right and what is wrong, and this is what I am quarreling with--is not that by and large you are not doing the right thing--I have no doubt about that. But when all of this is being talked about I get a little bit upset. Because we are forgetting a really important issue; that is, that really blinds us to all kinds of things--because Dr. Chalmer's papers are really an example you know about what's going on that is from a larger vantage point--that all kinds of wrong things are being done if one takes Dr. Chalmer's position, which I happen personally to endorse. But nobody would know whether its wrong unless one has established some criteria. And this you don't have either; you don't really have criteria, beyond the general criteria of good medical people. But by and large there are so many things that are going on on the outside, really go wrong, but really good people too. They are really not people who are (garbled).

Simultaneous discussion.

DR. KATZ:

As one of the issues, we really have to begin to learn how to educate the professionals--our young professionals. And both professions have failed this, law has failed in this, medicine has failed in this.

DR. CHALKLEY:

But until November of last year we had no textbook.

DR. KATZ:

Thank you. But we have to figure out how to train them, and that's awfully difficult.

DR. [illegible]:

Hasn't there also been an evolution in the ethics?

DR. KATZ:

Of course.

Simultaneous Discussion.

DR. BUTLER:

Even in the process of change there has to be at any point a set of reference points for the judgment of behavior at that point in time. I don't think you will ever be able to have answered absolutely any value question except by reference to the status of the value structure. You can interpret the status of a value structure at any point in time, by certain references as long as the references are clear. It's just like any scientific experiment. You can't ask the researcher to predict. . .you can make these probability judgments like this weighing one back there against another, but then they carry certain assumptions with them, also. When you use the term benefit, the term benefit isn't a term which can be easily quantified. It's a value term. When you use the term well-being, as a matter of fact when you use the term sick, these are not terms--when you use the term educated--and you ask the question--are you going to educate young physicians on ethical questions which in the process of giving them medical training. You may educate them on a code, or you may make them well informed on codes. But they can ask questions just like others ask questions, even outside of this charge.

DR. [illegible]:

I think I was saying that the value structure was changing. I don't know if you want to say ethics are evolving or not, but the value structure has changed. But I think Shelley mentioned just one example of what was considered acceptable 30 years ago which would be highly questionable now--whether catheterization would ever be permitted under present circumstances starting from scratch. Even though the original one was done on the investigator himself.

DR. CHALKLEY:

Look at the flap we had over amniocentesis.

DR. :

I don't think even digitalis would be permitted--would get by FDA if it were a new drug now. It has a very narrow margin of safety; it can cause all sorts of toxic reactions. (Garbled) So I think that there is a very

serious danger of getting so restricted as to be strongly detrimental to the people.

DR. KATZ:

That's right, and we are moving in that direction. That's what I see as one of the greatest dangers. But we have to begin--that is what I personally am interested in--to formulate some kind of system.

DR. CHALKLEY:

You cannot give--how many states know where you have to give 1/10th of 1 percent silver nitrate to a child.

DR. KATZ:

And things like that. Sure.

DR. CHALKLEY:

How about the states that still require vaccination and suffer the deaths from. . .

MR. BROWN:

Let me ask a specific question. I've been going to subcommittee meetings for most of the day today and Panel meetings for the last few months. And although I know that this particular subcommittee has a certain charge, I think we can't help but get some overlap when we inter-relate all those things because we started from a basic kind of Panel purpose. And I recall that after the Tuskegee Syphilis Study became very public--I guess towards the end of this summer and the Panel was appointed, and Dr. DuVal made a statement, that I thought was a good statement at the time, I don't know--some may consider it a little bit intemperate now--but, he said at that time that basically he was apalled by his knowlege of the study and a study like this could not happen now. And I would like to know why it could not happen now. What kinds of things are apalling about it; what would stop it in the system of checks, reviews, and balances from happening now?

MR. MANGEL:

Ron, before you get an answer though, you should describe the Study as you understand it. Because Dr. DuVal was responding to one set of facts; whereas that may not have been the situation. So you can't really answer that question unless you know.

DR. BUTLER:

. . .as they understood it at that point.

MR. MANGEL:

Now, if at that point, there was a conscious proposed treatment, of the known treatment, from participants.

DR. :

Of known benefit.

Simultaneous Discussion

DR. BUTLER:

Of benefit, because there was some question about the benefit of treatment.

Simultaneous discussion.

MR. MANGEL:

Because the policy says outright, the policy says you may not withhold known treatment--whatever, if one of the subjects develops a pathology to which treatment is available.

DR. KATZ:

The crucial question here.

Simultaneous Discussion.

DR. KATZ:

One aspect of one question, and that is the crucial question to which Dr. Chalmers alluded when he compared research and therapy. And that is the issue of how do we select our subjects. That's to me a crucial factor in the Tuskegee Study, and a great many other studies. I just read through--I'm now living a quarter of my life in Washington, so I have to return to my ivory tower--is--this was presented to me as an ideal study that was done by one of the Institutes here. And after I read it through, I had a long discussion with them--is how did they select their subjects for the study. And what did they tell them, and what did they keep from them. And we really haven't learned yet, to figure out what we can withhold, what we must tell them, what "therapeutic privilege" or human privilege, or whatever you want to call it, begins and ends; what authority we have to withhold, how to select them, etc. That I think is very much of an unresolved problem. And to that extent the Tuskegee Study is being repeated over and over again in all kinds of clinical research. How to figure that out I guess will occupy many of us for many many years to come.

DR. CHALMERS:

Well, to get back to the question of what is to prevent this from happening again.

MR. BROWN:

And leaving aside Dr. DuVal's comments; just taking the Tuskegee Syphilis Study, as you know it.

Simultaneous Discussion.

DR. CHALMERS:

My feeling. I think that the procedures that some of the columnists have described and those that are given in our regulations to grantees indicate two things. That if in fact the study was one that was not justified on risk/benefit ratio and all of that; and obviously it was decided there was no informed consent, and so on; but leaving that part aside, because informed consent, as I think I said earlier, was not really a part of the mores at that

time. I think, assuming that the study was one that was not justified inherently on the risk/benefit basis that we described; it was reviewed by a committee competent to review such a project; would not happen either in the Public Health Service itself or supported by the Public Health Service. Now I can't go beyond that because I don't know what other ways a study of that kind could get going. I would say that currently most such studies are supported by the NIH. I don't think it would happen in the VA.

I think it would be worthwhile--let's hypothesize that CNS Syphilis is still a common disease, which it is not, we don't see it very often anymore. And that penicillin reactions are more common than they usually are so that a serious physician would say, "Gee, I wonder if once you diagnose the patient as central nervous system syphilis, if he isn't so burned out, and maybe have some criteria for being burned out, that adding the danger of penicillin would really make him worse rather than better." If he then said, "Well, I will find that out by following these people untreated," it would be totally rejected by all of us. Not necessarily for ethical reasons, because he might be right, it might be better to follow them untreated. But it would be rejected because it's poor research and it's unethical to do poor research. On the other hand, if he said I think there is a serious enough chance that penicillin does more harm than good in treating these people, and therefore I will randomize the patients so that half of them get penicillin and half of them get placebo or expected therapy; and I will follow then each group carefully; and I will look at them frequently; or have a peer group look at them frequently to see if one of them is getting better than another; and I will stop to study if such and such a difference exists so that I wnn't be harming anybody any longer than necessary--I'll get informed consent from the people--I'll explain to them everything that is involved; and while I am doing the study because I don't really know whether it is better to treat or not; and I have presented it to a peer review group who agree with me that the knowlege isn't available as to whether to treat or not. But under those circumstances the study would be not only ethical but scientifically valid.

DR. :

Excuse me. May I point out one point about progress. And I think whether we all agree or not, that there's been progress in ethics, there clearly has been progress or at least new knowlege and new techniques in clinical

statistics and in the actual formal design of clinical trials, such that decision making theory for example or the use of automated computers for calculation results and other things of this type, in the kinds of decisions that Tom was talking about, about when to interrupt the study and so on, were actually not available 30 years ago, and are available as techniques today. And I think that is an important distinction.

DR. BUTLER:

Well, several things come to mind. The focus on central nervous system syphilis was again one of the things that came about in the process. They were studying syphilis, and there was a question of how this became. . .but, strangely, in 1969, there was a meeting here to review that situation, and with all of these resources you are now talking about, it wasn't terminated then. I'm still interested in what might have transpired in terms of weighing the decisions. You know, I can see much more clearly, or I have a sense of the historical setting in which there might have been an overriding concern for benefits out of the context in which this departure, this study, really was a departure from the treatment demonstration program and from what was going on both here and in Europe. I can see how that might have come out; and how it might have gained the momentum, but two things happened which I find a little bit puzzling. That after a large amount of data was assembled and even the autopsy data was assembled, one of the researchers asked the Surgeon General if he would invest $150,000.00 or so, which he estimated, in bringing together all of this data so it could be evaluated to determine whether there were any benefits to be derived from it as was earlier anticipated. Now this was before the 1969 decision to continue the study. This decision, apparently on the basis of money, was rejected. You know the decision to assemble and re-evaluate data; and yet after that time a decision was made to continue the study apparently without considering the request was already rejected. This is a little puzzling.

DR. CHALMERS:

I would like to know what stopping the study has meant--that each of the people who took part were called in and given penicillin?

DR. BUTLER:

No. What was recommended was that the study as related to untreated syphilis, be terminated, and that the patients be given an evaluation for their health condition, and whatever is indicated. . .

MR. BROWN:

It's possible that that would be a method of treatment, after the evaluation.

DR. [illegible]:

The one factual answer that I think I can give you, and it may not be factual at all, but it may help a little bit--is that when the Surgeon General sent out his request that subjects begin to have protection in 1966 or '67, the statistics I've been told, and I am only quoting them, is at that point in time 6 or 7% of all the grants coming into the extramural program were considered to be unethical. But since that time it has fallen to about 1%. So that I think that the rules and regulations we now have, the procedures we. . .

DR. CHALKLEY:

But you aren't talking about an extramural grant, you're talking about an intramural program operating out of CDC in Atlanta.

DR. BACKUS:

Yes, but we were talking about a climate.

DR. [illegible]:

I can tell you that within this institution I think that such a study would not be approved. It wouldn't be approved for the reasons that we've given.

DR. :

But a study in which treatment of questionable ethicity was withheld from (garbled) the population would be.

DR. BUTLER:

Well, is there any substance to the present announcements that there is a new epidemic of venereal disease, both syphilis and gonorrhea, in terms of its proportion in the population, and particularly in the young population? Is there any substance to this?

Simultaneous Discussion - Sure

DR. CHALMERS:

But it is a different situation from before because the average patient receives penicillin about once a year for sore throats and everything under the sun, and I suspect that the amount of tertiary lues that comes from this will be pretty minimal.

DR. :

And also, it is a lot more acceptable to go to a doctor and say I've got VD.

DR. BUTLER:

Yes, but it was acceptable then too. There was no apparent social stigma. I'm talking about the benefits to society which were medically indicated as benefits. In the context of another question, should all of this have been terminated when penicillin was introduced? This is one of the questions, should it have been terminated at that juncture? Now this is almost 20 years since penicillin was introduced, and you have another large scale social problem as was the case then with the epidemic proportions of the disease. Now, is penicillin making any difference in respect to that? Because, that was designed hopefully to become a pattern for developing a preventive program, you see.

DR. BACKUS:

Most of the people you see here are not that closely tied to the Venereal Disease program, so I think you could probably get a better answer from a neurologist, but if somebody wants to try to answer this. . .

DR. WOLFF:

Yes, but as an infectious disease person, I think I can answer that. To answer your question, I think that penicillin is certainly having an effect, probably will on the long-term outcome. The kinds of artery disease we used to see with syphilis, the kind of dimension we used to see, I think that the epidemic is still there, but certainly penicillin is not containing it, except in the sense that it might be far worse if we didn't have penicillin.

DR. BACKUS:

You have a medical answer to the problem, but you don't have a sociological answer.

DR. :

Well, it's not only that. We don't have a preventative. Once we have a vaccine for example, we won't need penicillin, there won't be a problem.

DR. BUTLER:

And there are presently efforts, at least--aren't there?

DR. WOLFF:

There are efforts underway to try to understand more about the gonococcus and the treponeme called syphilis and try to understand its immunogenesis and that sort of thing; but there is not presently anything on the horizon, but we think that there is a potential for it in the future, yes.

DR. BUTLER:

Are there any parallels between the introductory--are there any human subjects in their search to develop this vaccine.

DR. WOLFF:

Not at this point.

DR. BUTLER:

But at some point they would have to.

DR. WOLFF:

You see, you are hampered with these agents because unlike a lot of the viruses we work with in bacteria work, you can't cultivate this.

DR. BUTLER:

Yes. I know. (Simultaneous Discussion) . . .organism or something that might be found similar to this. Incidently, I was interested in just a little over a year ago, we have a leper colony in Louisiana, one researcher has discovered that the armadillo of all things provides the ideal model for the study. At some point she is going to have to turn to the human subject; and at some point everyone of these things has to turn to the human subject. It isn't the question of whether but it's the question of how; and it's a question of whether or not all of this activity by this committee can make a contribution on the, hopefully, on the positive side of the question of how, and the ethics related to the how. Whether we can lend some light to the whole area, certainly can't answer it by saying there can be no regulation, or no concern about the ethical, or mention of this.

DR. BACKUS:

I wonder if this is a good point for me to say it's now 4:30 almost on the dot. Dr. Allen's here. I think that we ought to plan for a little break here in a few minutes; and then those of you who would like to stay, you are welcome to stay. We're going to go into the extramural aspects of this policy; your contributions would be very worthwhile and helpful, I am sure. We will pick up then with the extramural side of this whole issue after Joel asks his question, and if anyone else would like to ask a short question--go ahead.

MR. MANGEL:

Dr. Butler's discussion of the decision to be process in 1945 period suggests we had a breakdown or problem in the review mechanism as much as in the surveillance mechanism. And again and again the General Counsel's Office, when this problem tends to be not so much in the initial review period, but in the after period, and there's been adopted elaborate procedures for peer review of initial protocols. But I don't see, at least in the grant field, and I heard a discussion of the six year required re-application peer review. And don't you thing--my question doesn't presume a dishonesty on the part of the researcher--but maybe the same fervor that is somewhat suspect when he submits

his initial protocol, should continue to exist. And don't you think we could stand a little shoring up of the surveillance procedure for the same reasons?

DR. CHALMERS:

I think we all agree with you. And our problem is mainly one of workload; figuring out how to do it, and still get some research done.

MR. MANGEL:

The same thing applies in the grants area.

DR. CHALMERS:

But I think we all have that uneasy feeling that. . .

DR. BACKUS:

You see, that is part of the gearing in process. Grants do come in for annual review. In order for an institution to submit it, we gear in the assurance mechanism to that annual procedure. I gather that you don't have a similar kind of review mechanism in effect here at the Clinical Center.

DR. CHALMERS:

Well, I don't think they go through the Clinical Research Committee every year, before they come in for renewal. At least, they never did.

DR. BACKUS:

Do you have an annual review--an annual requirement for annual review?

DR. CHALMERS:

Oh, I'm not talking about intramurally now, I'm talking about extramurally; when the university resubmits every year their annual request for renewal of the noncompeting grant, it hasn't as far as I know--does it say it's gone through--

DR. BACKUS:

It has to go through the local institutional review. Every year it has to go back to the committee. It must be certified that it has been through committee review when that application comes in for the annural request. Now it may be pro-forma; and that's all right, but it has gone through review.

They at least have had an opportunity to say let's take another look at it.

DR. ALLEN:

I think that's too simple an answer. It's proforma because there's no change in the project. If there is any signficant change of any sort then it does go through review.

DR. BACKUS:

That's correct.

DR. CHALMERS:

What Joel is going to ask you now, is how do you know if there has been any change or not.

MR. MANGEL:

I think the Clinical Center has the same situation. Any researcher is obliged, if there is a signficant change, to come in. The question is--how suspect is the researcher's judgment. If it is suspect enough to require peer review on the initial submission; isn't it just as suspect that he comes to a point, critical to his research and he has to double the dose; isn't his fervor still suspect.

DR. WOLFF:

You can't double a dose without getting permission, first of all; and second of all. . .

MR. MANGEL:

Well, perhaps that was a bad example.

DR. WOLFF:

. . .and he doesn't live by himself. He lives in a sea of people.

MR. BROWN:

Yes, but what I'm concerned about too is not the changes that have taken place internally in running that study or experiment, but what kind of changes might have taken place externally which that little review committee

at that hospital in--wherever it happened to be--might not be aware of.

DR. HILTNER:

Dr. Chalmers, I have one question--do I have time for one more?

DR. BACKUS:

Take all the time you'd like.

DR. HILTNER:

I stepped out for a few minutes, and if this has been discussed I would like to be stopped on it. But it still really has to do in a way with my earlier question as to the relation between medicine and health concerns. I might phrase it this way to make it a little bit more concrete. Suppose that someone in your Institutes here proposed a project that is for these purposes (I'm relieving it from the outside/inside kind of thing), proposed a project for studying what happened--two people who had come in here with diseases so serious, that is many of those where the ordinary physician hadn't known what to do and so on, and it's not necessarily that you're vertical men, but by having the specialty sources that you have here you have succeeded in restoring life, and some degree of functional life too, to persons who other wise might have dies. And who, before they came in here, might very well have begun internally the whole psychological progress of preparing themselves for death. Now, suppose one of your Institutes wanted to study what happended to people of that kind--which obviously would mean some kind of inspections upon admission, etc., and follow-up. Now, I personally know some people of this kind--not necessarily who have gone through this Institute here--but other places; who psychologically prepared themselves for death. Who have then by modern medical means of one kind or another been spared that. Who have become psychotic. Now, who is to say that this is a result--I'm not prepared to say that--but I mean sequencially, a chronological sequence, can become psychotic. The thing I am getting at is, would you regard it as the medical concern to deal with the presented disease regardless of other considerations? Or would it also be a part of your research interest--assuming all other aspects of the thing were set up appropriately and the controls and so on of the ethical controls of the kind you have been assuming here were involved. Would that be of interest to this Institute, or would you regard that as non-medical or trans-medical or the business of people other than the National Institutes of Health? I think you see what I'm getting at.

DR. CHALMERS:

Yes. I think that we have to be interested in what we do to the patient, no matter whether we do it to them here or later. Hopefully the committee, if the man himself, the investigator himself didn't concern himself with that. The Committee would raise questions about it and have to be satisfied with improvement. But if you ask if we then later on pursue what's happened to all of these here to see whether something we didn't anticipate or didn't think at the time was worth pursuing or. . .

DR. HILTNER:

No. I'm not necessarily faulting you on that. I think that that would be a whole other kettle of fish. But I'm thinking of a researcher or research institute wanted to make a major project out of follow-up, which would of course also require something new to begin with, of a certain group of patients. As you say this would be limited, so it would be a project and not everybody. Would that be a medical concern or transmedical concern?

DR. CHALMERS:

Oh, I think that would be a medical concern.

DR. HILTNER:

So that the Institutes, if some of your staff people were interested in that, that would be kosher?

DR. CHALMERS:

Sure.

DR. HILTNER:

Well, I'm very relieved to hear that.

DR. KOPIN:

There is actually a similar type of study--the psychosis that accompanies cardiac surgery.

DR. HILLNER:

That is being studied here?

DR. KOPIN:

Yes. People at NIMH are following that study.

DR. BACKUS:

This is a good reason for retaining the NIMH as an intramural component of NIH, I assume, because of the opportunity of expanding into these areas.

DR. KOPIN:

I would think that this would raise one question, and that relates to our procedures that have been described in so much detail. And that is that I think we do have a problem occassionally in defining what is a research project and the example that you give I think is probably the kind of thing that I would think the terms of whether such an example would come to peer review might be quite variable.

One sets up the study. The study is subject to peer review. If it's a diagnostic or therapeutic study then it has peer review at the level of the Institute. If it's a study which would be interpreted as a non-diagnostic, non-therapeutic procedure, then it would go through the full procedure that you've heard about. But, I think all studies, suddenly if they find that an aspirin is causing a new kind of rash, you see this, the first time you make the observation we can't connect the two; the next time you say, yes, the patient had aspirin, the second case--I wonder if aspirin is doing this. Then there is the formalization of the study plan, but one can't anticipate every time one gives an aspirin that one might encounter some new finding. Once the new finding is made, once the hypothesis is developed, testing the hypothesis is the project. I think that we can't anticipate all hypotheses. One can only develop the project around the hypothesis. But once the hypothesis is developed and then it takes the format of a project which is subject to peer review.

DR. BUTLER:

Is there any progress on the same area. You mentioned one thing that was specific in respect to the initiation of the Tuskegee Study. And that was you cannot retrospectively establish controls. Is there anything technology

of a--such as computer models or something like this--which can substitute for or thinking of substituting for human controls, such as making a retrospective study possible which is scientifically rigorous enough to. . .

DR. :

I think the answer is a qualified yes. That really the judgments are not quite as refined. If a disease is universally fatal and a new treatment is introduced without controls, and all the patients recover in the extreme instance, then obviously no control would be necessary. On the other hand, in most instances where this is obviously not the situation, and the problem that still has to be addressed is--well, did the disease change in some way, were these strictly comparable, were we really dealing with the identical disease, did some environmental circumstance occur which altered the course or historical perspective. I think these are all legitimate questions.

DR. BUTLER:

I was just trying to determine whether or not there is developing anything--like models--on the basis of the human experience of the whole profession?

DR. :

I don't think, unless you take the example of the either/or situation, I don't think there is. I think you still have to use the control's job. You can sometimes use the patient as his own control.

DR. BACKUS:

I've just been informed by Dr. Chalkley that he has a problem coming up around 5 o'clock; and it's a quarter to five now. And he was one of our key people for the continuation discussion. Let me ask the Panel if they would mind just going ahead with this discussion that you're in now with the understanding that we would probably set up a meeting later--a subcommittee meeting later--to go into the extramural programs. And take the time at that time to go into the problem at greater depth. Any objection to that? So why don't you just proceed, if you would.

DR. BUTLER:

Extramural programs, because I know that there are. . .

DR. BACKUS:

We might get started on it and get a few questions in. All right, why don't we. . .

DR. BUTLER:

Actually, we need as much as we can get whenever we have the opportunity to get it.

DR. BACKUS:

Well, this is our opportunity to get a little. Dr. Chalkley and Dr. Allen are here representing the extramural programs of the NIH. Now you gentlemen can stay if you like. . .

DR. BUTLER:

On behalf of the committee, I would like to express our appreciation, our very deep appreciation for your responsive information we have gathered today. We will certainly take time to send you letters of thanks. Thank you so much.

DR. BACKUS:

Well, we can certainly get started on this and what we can't gain from this short session we can plan to make use of in setting up another subcommittee meeting of a later date if we feel that that's needed. Don, would you--I think you can sort of pick it up from where we left off, if you would like.

DR. CHALKLEY:

All right. I frankly don't know quite when the NIH, the Public Health Service, began its clinical research programs. I imagine that there were some back in the early 1900's and I know when I came here--when I first knew about it--my father came to work for them in 1929. They did have some clinical research going on in university facilities, and there were at several times clinical NIH/PHS control clinical facilities in Boston, California, and, of course, you're aware of the situation in Ohio and elsewhere.

There was no real extramural program however until 1937 when the National Cancer Institute Act was passed and the NCI began giving out grants. Between 1937 and approximately 1947 the National Cancer Institute gave out approximately 300 grants. I read them over years ago--298 to be precise. There were none of these that involved clinical research; there were none that involved, directly involved, human subjects at all.

To the best of my knowlege, the first activities involving clinical research began roughly back in 1945, when we picked up some ONR projects which did involve some malaria studies, some VD studies, and these involved--but they were still not clearly separate from practice of medicine and service. And as far as I know we had no patients in hospitals involved per se--a lot of clinical services but not much hospital research until 1947.

In 1947 we began our first grants which involved payment of hospitalization expenses and the first very serious clinical research which originated in that year. I remember that date because the gentleman who started out was Sidney Farber--he asked for hospital expenses and someone said can we properly pay hospital expenses, and the reply was--if you can pay for rat bedding, you can pay for a bed for a human patient. And with Sidney Farber's work in the Children's Cancer Research Foundation in Boston, began our really serious involvement in research involving human subjects. Again, Sidney Farber was practicing what might be called poison gas therapy using mustard gas, a treatment of nitrogen mustards, methotrexate, in the treatment of leukemia. The number of grants in 1947 was probably--what was it Ernest, back in the low hundreds?

DR. ALLEN:

Yes. It started with roughly 50.

DR. CHALKLEY:

They introduced at this point the National Advisory Health Council, The National Cancer Institute worked from the National Advisory Cancer Council, and you had a total number of grants not 300, but you were now getting up into the several hundreds a year. And this continued, of course, on through--put in a couple of key dates--1962 was a key date for several reasons. 1962--the Kefauver Hearings on the Food and Drug Administration (FDA) Acts. And also

it was, if I remember correctly, the year of the Southam-Mandel case. It was in the latter part of '62. Chester Southam went over to the Jewish Chronic Disease Hospital and persuaded Dr. Mandel, Chief of Service there, that they could properly and needed to transplant tumor ceels into patients. So this is also the date of the Southam-Mandel Case in New York City.

Late in that year, in 1962, the Surgeon General, following the Kefauver Hearings, and with the first rumblings of Southam-Mandel beginning to make their way southward from New York City, in consultation with the then Director of NCI, decided they had better look into what the NIH and the Public Health Service as a whole should do next. This ran to two or three studies--I won't go into the details as to what came out of it--what the complications were--but the ultimate answer of two successive committees was that basically, as far as the grants program was concerned, we should do nothing. That the grant was a gift to the institution; that if you give a BB gun to the boy down the street, and he absentmindedly shoots a girl across the way and blinds her, the fault lies not with the giver of the gift, but with the boy who pulled the trigger. And this was the basic attitude. It is we who receive the money who are responsible. We are the people who will be sued. The Government cannot be involved. The Government refused to be involved in the Southam-Mandel case on the grounds that the grant was a gift. The persons who committed the injury were not employees or agents of the Public Health Service, but employees and agents of Jewish Chronic and of the Sloan-Kettering. And the Government was not involved. And on this basis, said the institutions, the Government should require us to do nothing. We should be fully responsible. No action should be taken by NIH. This position, the Surgeon General and the Director, NIH, refused to accept. In 1965 the first step was taken. This was an instruction to all of the advisory bodies.

DR. :

You said they refused to accept--whose position was that?

DR. CHALKLEY:

The position was recommended to the Surgeon General and to the Director, NIH, by the Livingston Committee and by subsequent subcommittees--outside people. It was a mixed committee, inside/outside. And in '65, I guess just

in the beginning of that year, the last subcommittee came up and said, well, there are three or four things you can do and the instructions were--one of them I think Palmer Saunders who is head of the Research Grants Review Branch, said that they would implement immediately; this was an instruction to all of our study sections that if they came across anything that appeared to raise an ethical issue, or an issue of hazard to subjects, they should call this to the attention of the councils immediately. They should make a specific note to this effect. In the past our scientific review bodies have been informed that their sole concern is with scientific merit. And you, in a sense, seize your authority--as I did on several occasions--by calling attention to what appeared to be hazardous. These were considered policy questions, not questions of scientific merit. There were several executive secretaries in the study sections who did this more or less habitually. But in '65 we made it official. And from then on you began to see bursts of problems. Now what happened in the middle of 1965; '65 was the first order to ask study sections here to watch for ethical problems, and I would say that this in a sense was the first official expression of awareness of ethical problems involved in grants supported research here at NIH.

In the middle of 1965 three applications came in here--to two different study sections and one council and they were all involved with primary myocardial disease, which is very characteristic of alcoholics and it's found in large community hospitals. It's found largely among the disadvantaged. And these studies were to go on in three large municipal hospitals in the United States and they involved a variety of mechanisms of getting at damaged tissue in the heart. One of them was going to run a suction tube down through the carotid to the heart, apply suction, nip off pieces of the inside of the heart, and carry out some very routine studies on it. The second man was going to use a biopsy needle and go through the chest right into the myocardia and carry out some very simple studies. In the third one they were going to make an incision up here in the chest to visualize the outflow tract of the heart, take two or three samples and do some fairly sophisticated bacteriological, viralogical and other pathologic studies.

The first two were disapproved by study sections scientifically and approved otherwise with the understanding that the principal investigator and the principal investigator only was to obtain the informed consent of the subjects. I won't go into the reasons why that particular caveat was put on there, but it went to council, and there was a knock down drag out battle that lasted for about two hours, in the course of which one member of the council refused flatly to be associated with the approval, and said he was going to the Director; he was going to the Surgeon General; and he would go to the President to block this study being approved. As part of a compromise with the Institute, there was an agreement that they would obtain a special assurance--a special assurance, lower case--from the institution to which the grant was given. They recognized the hazards, that they would ride herd on it, and that they would assume responsibility for anything that went wrong. This was conveyed to the NIH in the middle of 1965. The NIH formally adopted this practice of requiring assurances from any institution where there was a special hazard. Of course what constituted a special hazard was clearly left up to the review bodies.

This didn't appear to be entirely satisfactory, and in the middle of '66 there were letters from Representative Gallagher from New Jersey, who was concerned about, not medical problems but privacy. And there was a letter from Senator Javits--and said have you done anything about informed consent since this was brought up in the Kefauver-Harrison in 1962. The Surgeon General said, we shall take it to the National Advisory Health Council later in the year. They did, and then in the beginning of the following year we issued our first formal policy. And we need not go through the one that was issued in--there was one February 1966--there were promptly two modifying memoranda. We completely revised the policy, tore it apart, put it out again in July 1, 1966, followed by four more modifications. Then it was revised again in the middle of 1969, based on our experience in the two preceeding years, and then at the time that that came out Dr. Allen suggested to the Under Secretary, HEW, that it should be applied across the HEW as a whole. There appeared to be some problems with this, so we took the policy apart once more and in your folders is a copy of Grants Administration Manual Chapter 1-40, which outlines the policy in its present form. So we've had revisions in '66, '66, 1969, and 1971.

The basic policy has changed little during that entire time. The changes are largely changes in detail and implementation of the policy. The do not change the policy as such. The policy states flatly what the institutions said all along, that the responsibility for the protection of rights and welfare of subjects belongs with the grantee, because they are responsible for the performance; they are directly in contact with the patients; they are the people who select the patients. They are the people who hire the physicians; control the facilities, and these physicians are licensed in the states in which the situ-institution lies. The physicians are licensed in those states, the hospitals are licensed in those states, and the laws that apply are the laws of those states. Therefore the placement of the responsibility should lie in the local institution where the funds are used. The policy then goes on to say--in order to insure that this responsibility is properly carried out we require that the institution establish a local review committee, and that the committee review all projects which involve human subjects at risk--and at risk is defined as anything that is done to the subject other than that which employs standard and accepted methods for his good and his good along--anything that involves a human subject at risk has to be reviewed, to determine that there is adequate protection for the subjects right and welfare, that the benefits will outweigh the risks in the project, and that informed consent is to be obtained by methods that are adequate and appropriate. And it also goes on to say, incidently, that the DHEW is also concerned, as well as the institution, that the application for support, be it a grant or contract, will be subject to further review by DHEW.

It is sort of a dual review system, two different types of review. One is the institution's review, which you are aware is expected to be a very broad one, even if it's a medical school or a medical hospital. You're going to have surgeons, you're going to have internists, presumably pathologists, other positions, and in addition, at the moment, in a hospital situation, because of Food and Drug regulations, we require that certain of these individuals down here be persons other than physicians licensed to administer drugs. And as a consequence, that means that practically every medical institution you have on the list now has down here some people who are not physicians.

These may be gynecologists; they may be scientists who are not physicians, scientists who in the most part are outside individuals--outside the hospital, what the FDA terms laymen. An FDA's layman is anybody who is not licensed to administer drugs, which covers a very broad spectrum.

On our committees of course--when an application comes in here and deals with research in surgery it's going to go to another committee that's all surgeons; if its in pathology it will be almost all pathologists, or at least an adequate concern with pathology; and if its in psychology it will end up with a group that is almost all psychologists. Review here is in depth. The review at the institution is across the board. They are not the same reviews. But the chances of an application which is not generally acceptable getting through reviews of both types is very small. I would never say that it is absolutely nil, that there will be no problems, because we have had applications that went through review at the institution, and were cleared, and went through review by a study section here, and then by a council here, and then by staff here, and then went back to the institution and were turned down on the second round. Because they had learned things in between that time that they didn't know when they first reviewed, that we didn't know, and that they found out between times. Times change. And We have had projects for instance that involved a variety--where science has changed--and science can change in approximately the six to seven months that it takes us to review.

The review required is very similar to that which is required by the British Medical Research Council, AMA Medical Research Council, and the Australia Medical Research Council, except for one apparent difference. None of those require continuing review. It is reviewed once by peer review. There is no requirement for continuing review. We do require continuing review at least annually, and this is the thing that makes the difference more apparent than real, because in Australia and Canada they only give grants for one year periods. So the fact of annual review is built into the mechanism, and the difference is not quite as distinct as it may seem. In order to provide for the review mechanism, what we require at the moment from our major institutions is what is called a general assurance. This is a document which states how the institution will carry out the review; describes the committees; describes the review structure; frequency with which they'll meet, and so forth and so on. The

assurance, as the document comes into us, may be four or five pages thick--the one from University of Missouri is two inches thick. This, of course, in the thickness, is a function of whether it's on both sides of the paper, one side of the paper, double-spaced or single. But they are quite compendious documents in most instances. They describe a procedure, and this is basically a procedural policy. It requires a review--it says that you must review. It does not say what you must review for, but at no point does it say what you must do, what you shall not do, what is ethical, what is unethical, what is good, what is bad--it simply says, go in and use your quality judgment. Look at it in terms of, local laws, local standards of medical practice, local standards of community acceptance--we are not going to try to sit in Washington and dictate what is going to be acceptable to Cuban refugees in Miami, to French Canadians in Maine, to Indians in the State of Washington, or to Mex-Texs along the boarder in San Antonio, or to Blacks in Watts, or to Blacks in the north side of South Bend, or to Blacks in the south side of South Bend--and those incidently are two entirely different groups--or the ones in Cleveland, or the ones in Jackson, Mississippi, or Tugulu. But these are all different groups, and the people who should know them are the people in the site. It does not at any point define, describe an ethical policy. It states simply, list all the ethical policies of which we know, of which we are familiar--we try to keep people up to date on them. Now, as to what this does.

At any one time, we have gone through the present Public Health Service System--at any one time we have approximately 15,000 grants out, of which about 1/3 or approximately 5,000 involve human subjects. We get every year, about 15,000 units to go over; and again 5,000 of those involve human subjects. In 1966 Dr. Wolff mentioned, when we began the policy, about 7.2% of those 5,000 applications were raising questions in the minds of study sections, and about half of those questions, or I guess about 3.8% is the number that comes to mind, the questions were such as to justify disapproval of the application. In 1971 this number had dropped to about 2.2% of the total.

DR. BUTLER:

You say that between '65 and '71?

DR. CHALKLEY:

Between '66 and '71. There is only one other problem with this and that is in the last year this is up to about 5%.

DR. HILTNER:

That is turned down on what grounds?

DR. CHALKLEY:

These aren't turned down--these are questions.

DR. HILTNER:

Questions on what grounds?

DR. CHALKLEY:

Largely, undue hazards to subject. I think in all the time we've been looking at these--and we've got about a thousand or so projects picked out--I have seen three that I would call clearly unethical. A situation in which the physician knew that what he was doing was wrong and he was going to do it anyhow.

DR. HILTNER:

Now, that presumes some sort of ethical standard, that you're implicitly implying, but you had just said previously that you were not involving ethical considerations except descriptively.

DR. CHALKLEY:

No. We say quality institutions are required to identify an ethical policy. But basically I take the position that you are dealing with a highly ethical professional. And I do not think that you will find any very high percentage--I think, actually, less than 1$ of the applications which are questioned by study sections are in my opinion clearly unethical. The rest of them are matters of ignorance, and poor judgment.

DR. HILTNER:

But then, that would imply that you have a broad based kind of ethic which can permit many variations within it. Well, now is that stated?

DR. CHALKLEY:

That's right. No. It simply goes flatly and says that we prescribe no code of ethics.

DR. HILTNER:

But you really do.

DR. CHALKLEY:

We expect that they find something. Because obviously in a medical school some institutions can live with the Nuremburg Code, others, most of them medical institutions will go out and pick out the Declaration of Helsinki. And there are institutions, Harvard University developed its own. Harvard actually has two or three, depending upon whether you're talking about nurses, medical school, or the use of students. There are institutions which--of course, we have a lot of institutions which have no medical activities--activities largely psychological. And the APA Code is applicable, or an institution like the New York School of Social Work which has grants funds and so does the American Society of Social Work. But in the majority of instances there is a code--medically speaking it's going to be Helsinki as a general rule. And a few of them will use a modified Nuremburg--the Nuremburg is inapplicable in any research that involves children.

DR. HILTNER:

What I'm trying to get at--I don't mean to take you the wrong way, but you said that you had looked over a few which in your judgment were clearly unethical. Now in making that statement, what kind of criteria was in your mind.

DR. CHALKLEY:

If you look at the projects, the objections that were raised in the study section are principally technical objections. They are rarely that a

study section will say that this is unethical. A man comes in and proposes to feel parasites to some student volunteers--but he believes that those parasites are harmless to the volunteers. He wasn't aware that they could result, and probably would result, in blindness in about 1/3 of those youngsters before they had passed another twenty years. We have had Board certified hematologists propose projects which on the surface of them looked absolutely lethal because they were ignorant.

DR. HILTNER:

You don't really mean that. You mean that you looked at them and that they would bring bad results.

DR. CHALKLEY:

They would bring bad results--fatal results.

DR. HILTNER:

Well, how would you define that--any kind of project that might be proposed that wouldn't harm subjects from a medical point of view, but which might still be unethical from your point of view.

MR. MANGEL:

Give three examples.

DR. CHALKLEY:

The institution here that proposed to run catheters in both brachial arteries and then subject them all to work on a treadmill and if they were unwilling to volunteer, offer then $150.00 to do it, or $200, or $250, or $300, or $350 and offer them as much money as they would until they were willing to go. Or the individual who told us flatly, we will not utilize informed consent, we can't get informed consent from these people, so we aren't going to tell them. Or the man who accepted a grant from us to do anatomical work and then went out and did physiological work and was telling his patients that this was being done for diagnostic purposes--it is the same thing they did in Southam-Mandel case--this was being done for diagnostic purposes, when as a matter of fact it had no diagnostic purpose as far as these patients were concerned. That I would say was clearly unethical.

DR. HILTNER:

On what grounds--what would be your grounds for saying this?

DR. CHALKLEY:

He was deliberately misinforming the patients.

DR. BUTLER:

He was lying.

DR. CHALKLEY:

He was lying--deliberately misinforming them.

DR. HILTNER:

So it is not the money you are objecting to really.

DR. CHALKLEY:

No. The money--well in the other case, the money--this is coercion. I would agree in this case--there is absolutely no question--this is coercion. Because if people volunteer for it, he won't offer them the money. It is only if they refuse to volunteer then he will offer.

DR. HILTNER:

If it's strictly money, how is it different from offering free medical care in this institution.

DR. CHALKLEY:

This is a lovely question that Dr. Wolff answered the other day. I can't answer that--whether this is a problem of any research carried out in a charitable institution--not just this Center here, but any place.

DR. HILTNER:

You see, I understand your attempting to not have a legalistic code. I understand--obviously you have great sympathy for it--but it seems to me that you have certain kinds of minimum standards.

DR. CHALKLEY:

People keep telling us the language is too legalistic--I'm glad to have some. . .

MR. MANGEL:

But Don, the answer is that there are standards set out in the policy and they are both ethical and in the end medical standards which are going to superimpose--they are not dealt with specificity with any of these.

DR. BUTLER:

There are areas in which you cannot distinguish between the people.

DR. KATZ:

Dr. Chalkley, do you have faith in the Helsinki Code?

DR. CHALKLEY:

No. I have faith in the performance under it.

DR. KATZ:

But you can't perform under it--you have to have faith in the basic document.

DR. CHALKLEY:

Yes. I think that the only point is that you get people--you don't put the code out, I wouldn't put the code out alone, and say, everybody will adhere to this. I would put the code out and then I would ride herd on them. I think the fact that a man--I have no doubt that, to answer a question that was raised earlier, that there are a lot of studies that are proposed, that would be proposed if the investigator did not realize that he was going to have to go through this review mechanism.

DR. KATZ:

All the review committees that I know of leaving min aside for the moment, aren't working.

DR. CHALKLEY:

Aren't working?

DR. KATZ:

No. And good ones--major universities.

DR. CHALKLEY:

Aren't working in what sense?

DR. KATZ:

They are sending you them compendia--but they don't take them seriously.

DR. CHALKLEY:

I'm sure they aren't. I'm not in the least surprised.

Simultaneous Discussion

DR. BUTLER:

They are saying economic and social persuasions that any other group would be under; and this is where the central problem is.

DR. CHALKLEY:

Yes. And this is of course why there is an advantage to -- the answer why I firmly believe in the second review. And also, I think that one of our big difficulties is since 1969, my office has been unable, for financial reasons, to make any visits to these institutions to see why they aren't. Because there are some institutions where, I will admit, there are approximately 10% of the applications submitted to us that are being turned down in the study sections on grounds of undue hazards to the subjects.

DR. KATZ:

You have 5,000 human proposals a year now?

DR. CHALKLEY:

Right. Roughly.

DR. KATZ:

And how many people review these 5,000 proposals? How many groups?

DR. CHALKLEY:

How many groups?

DR. KATZ:

Yes, these 5,000 proposals.

DR. CHALKLEY:

Oh, . . .

DR. BACKUS:

That includes the NIMH grants?

DR. CHALKLEY:

Yes, you'd have to to get the 5,000. There are about 30--I think that's about right--because there are 40 committees at NIMH, there are 50 here, and I guess about 3/4ths of those I guess take clinical studies.

DR. KATZ:

About 50 committees? So that means about 500 proposals per group. And these are the groups that meet three times a year?

DR. CHALKLEY:

That's right.

DR. KATZ:

And they review 500 proposals?

DR. BACKUS:

A hundred.

DR. CHALKLEY:

The average study section will see something between 75 and 100 applications a round. And you will run 10 to 15 members.

DR. BACKUS:

But a lot of these he has been talking about will be disapproved on grounds--at least half of them if not more--will be disapproved on scientific merit, anyway.

DR. HILTNER:

But does this raise any question--maybe this is irrelevant--I'm not a physician. Do you raise any questions about what you were speaking for previously in terms of the bulk that these things have--that is to say--are you unintentionally, by trying to cover everything, contributing to a workload which then makes it virtually impossible for anybody but the guy who actually puts the report together, to master.

DR. CHALKLEY:

This is a very serious problem and I wish we could find our way out of it.

DR. HILTNER:

For example, universities now, in increasing number are barring student doctoral dissertations from being more than a certain length. Princeton University has now said, 250 pages with apparatus. And a dissertation exceeding that is not acceptable.

DR. CHALKLEY:

I wish they had told me that before I got mine--mine ran 600.

DR. HILTNER:

Well, but you see the point--that is, well frankly mine was 500, but I think that I would have had a better dissertation if I'd been cracked down on and made to reduce it.

DR. CHALKLEY:

No. The best ones we have--I'd say the ones we use as examples--in fact only run about a dozen pages. The University of Missouri is that thick because it has six campuses--and the procedure is described for all six and the schools vary quite a bit.

DR. ALLEN:

Now you are talking about assurances, not an application.

DR. HILTNER:

But you see, if you are putting as much faith in an institution, and its assuming final liability, as you indicate that it is.

DR. CHALKLEY:

That's true. That's were the suit is going to end.

DR. HILTNER:

Then, are you getting so much information, which fundamentally you might do without, if you follow the policy of. . .

DR. CHALKLEY:

No. I think that Dr. Allen is making the point that if you get an assurance from an institution, the assurance nominally is going to last for an average of about six years--this describes the system that presumably is being applied for review purposes. Now the same institution may turn around and submit to us 40 or 50 applications for research during the year and mentally those can run anywhere from about 8 to 10 pages. But the study sections are seeing are applications for individual projects.

MR. MANGEL:

The study section is Federal -- a group of Federal consultants.

DR. CHALKLEY:

That's right.

DR. BACKUS:

Dr. Hiltner, we get one assurance from a major institution dealing with a number of grantees, but each time an applicant applies to NIH on a research grant application involving human subjects, this receives the kind of review that we are talking about. And along with that we must receive certification from the institution that it was reviewed in accordance with the assurance they provided. Now, it's still a complex picture. I'm not trying to simplify it--I mean, I'm not trying to cover up the fact that it is still a bulky document from the institutions.

DR. CHALKLEY:

Applications come through of course. As I said, the thing that disturbs me--one of the difficulties with the thing admittedly it is a complex review procedure. I have no doubt from the number of turn downs that applications we're getting from some institutions--that they are not getting the review they should get. On the other hand, when LSU or when MIT calls you up in the middle of the afternoon and says we would like to withdraw so and so's application--they had some reason to do it. And LSU calls up and says, we will not approve any portion of Dr. X's application involving human subjects--there's no question review has been going on, and it's effective to some degree. There is also no question that we need the continuing internal review within NIH.

DR. ALLEN:

I'm sure you've visited these committees when they were reviewing them, and have seen them turned down. I have. I was surprised at your statement, because my experience has been exactly the opposite; they seem to be doing a completely thorough job and they are turning applications down in the committee. And they show in their discussions that they've done their homework before coming to the committee--they don't try to do it around the table. They have reviewed them. They come in. They exchange views. And sometimes a man who has thought he was going to vote against one, would change because of the discussion would show that he had to change his mind.

DR. :

How do you account for the recent increase?

DR. CHALKLEY:

Actually I find it a little disturbing. I suspect that what we've been measuring here, in a sense, is not improvement so much as the difference of the sensitivity of the review groups. The one thing we need to do now--and we will after these last two rounds--is to go back and see what's involved in this 5% increase. If we are still getting a drop in the disapproval rate, and in just looking at them, I think we are not getting any higher disapproval rate than we did before--we are getting more questions raised. But a lot more of these are being passed on to the institution. We do not seem to be getting any

significant increase in the numbers as that are actually being turned down. But the groups are a lot more sensitive, I think, then they were a year ago.

DR. KATZ:

Was Goldzieher's research reviewed by you?

DR. CHALKLEY:

No sir. That project came in from the Syntex Corporation on an investigational new drug application--Food and Drug.

DR. KATZ:

That went through FDA?

DR. CHALKLEY:

FDA.

DR. BACKUS:

Well, it was reported to FDA on their forms, but FDA can't keep up with their paperwork.

DR. CHALKLEY:

That's why he was raked over the coals for violating his protocol, which he did.

DR. BUTLER:

I don't know how our time is. . .

DR. CHALKLEY:

Well, mine's disappearing.

DR. BUTLER:

Well, I would like to ask directly: Do you feel that the existing policies, and certainly this means combined policies and factors which we just referred to, are adequate to protect the rights of patients who are engaged as subjects; and, I had another question.

DR. CHALKLEY:

I think the basic policy is a sound one. Like any such policy it needs monitoring and follow-up to ensure that its being properly interpreted in the field. This we do not have. It also--this is something we have recognized since the beginning--needs to be followed up with some sort of an educational campaign--and this, we have never been able to mount.

DR. BUTLER:

Our question is--the second question--are there any improvements to be recommended in the policies. To make an address to the implementation of policy.

DR. CHALKLEY:

There are details. There are small details that we are proposing to change; we expect to put the policy in the Federal Register within the very near future, and there will be some minor changes then, and we expect to propose some fairly major ones.

DR. BUTLER:

What are some of these even minor changes that you have?

DR. CHALKLEY:

The present policy requires, among other things, that the institution should not use exculpatory language in consent forms. This is waiving rights and responsibilities. We are going to change this to must. It says that the institution should have laymen on the committee. We are going to change this essentially to must. The language will be a little more complicated. There is a section in there now on the statement in the policy pointing out that the risks should be weighed against the benefits to the individual, or to the population in general. And this section has been misunderstood, misinterpreted, and it will have to be explained.

There's also, those I would say are minor, some fairly major changes that we are considering. The policy at present permits an institution to indicate not that it has completed review, but that it will carry out the review in the future. We are expecting to require that this review be completed

within a matter of days after submission of the application, at an early date well in advance. We are also proposing to put some language in there specifically with regard to compensation of prisoners or other individuals--payments to them in connection to the performance of research. We are also going to go back and require submission of the committee structure on an annual basis. There will probably be an annual report back to NIH.

DR. KATZ:

Are you going to do sanctions?

DR. CHALKLEY:

What?

DR. KATZ:

Sanctions?

DR. CHALKLEY:

The enforcement section in the back right at the moment is going to undergo some changes so we're in a position--there is one point in there that is not very clear--provides that we can terminate grants which we can--and we're going to rewrite that to make it a little more blunt; since I discovered from Mr. Mangel that we can terminate a lot faster than I thought we could. And it also provides in there for loss of eligibility for support of an institution that fails to comply. And there also should be a section there that allows (us) to terminate the eligibility of a principal investigator as an individual. So that if he gets bounced out of one institution, we can more or less follow him around; and we can suspend his eligibility to receive grants subject to the pleasure of the Secretary.

DR. KATZ:

With respect to institutions, are you going to have some definite provisions, under what circumstances the whole institution might not receive grants anymore, if the institutional review committee violates?

DR. CHALKLEY:

The language in the Public Health Service Act, and the language in here, is for the continued indefinitely in the public interest, until terminated in the public interest by the Secretary. It doesn't give a term. Basically, it would allow the institution to protest. And on the basis of the more or less adversary proceeding on the protest decide whether they could restore it.

DR. KATZ:

It's a continuation of this. I was recently asked about the following problem that arose at an institution, but the institutional review committee found out that an investigator had violated practices--their directives. What should they do?

DR. CHALKLEY:

Well, we haven't gone past privity in the institution that way. Dr. Cooley is no longer a member of the staff at Baylor University School.

MR. MANGEL:

I think that that's a perfect example.

DR. CHALKLEY:

Yes.

DR. KATZ:

But you had not the procedures. I went through the documents.

DR. CHALKLEY:

I would be inclined to leave that to the local faculties. If we found out it is a different matter.

DR. KATZ:

Should the university inform you? That's the question they posed to me.

DR. CHALKLEY:

That's a nasty question. I would say that this is up to their judgment.

DR. KATZ:

You would penalize them for not informing you at this point, under your regulations.

MR. MANGEL:

Our policy does require the reporting to the Federal Government of any changes.

DR. CHALKLEY:

There is nothing in there that requires them to report mal-performance of an individual.

MR. MANGEL:

I guess that what I'm getting at, is, it depends upon what the mal-performance was--if it was a change in protocol. . .

DR. KATZ:

No, no. It was very gross--that would be minor.

DR. CHALKLEY:

No, it was like Kantrowitz and the flap at Maimonides which never really came out into the open. They accused him of violating a protocol that he had submitted, but it was a very tricky business to have decided.

MR. MANGEL:

I would be interested in what the reaction among the administrators would be, but (it) depends upon the culpability of the institution. If it was something that was totally out of control and the institution reported it promptly, and it wasn't casued by a breakdown in the institution's procedures, I can't see how that would rebound to their disadvantage.

DR. KATZ:

What should they do now--that is the question?

DR. BACKUS:

Was anybody actually hurt?

DR. KATZ:

The protocol was originally written out because of the concern about people being hurt by this. Whether they were hurt, I don't know.

MR. MANGEL:

If people were hurt, I should think it would be incumbent upon the institution to tell us something about that.

DR. CHALKLEY:

I can tell you one thing, if he was using our funds, and they did not cut off the support, the policy does require them to cut off the support. This at the moment is the only club we have. And if they did not cut off that support and it was evident that they found the man in violation of their own regulations, in carrying out a project in a manner in which they did not approve, and they did not cut support off, I would say that institution. . .

MR. MANGEL:

But if the specific act were terminated immediately and the institution imposed its own corrective sanctions, whatever they were, and if you knew about them externally, you know, you would say that they were acceptable, I'm not sure that we would feel that we have . . .

DR. CHALKLEY:

And when they set the salaries, they hire the men, they fire them, they're not Government employees, I. . .

DR. KATZ:

No, I'm sure its quite clear, you know, under existing procedures this would not be necessary, and it would not be in violation of anything. Should that be changed as you are now looking over that section?

DR. CHALKLEY:

There is no opportunity for an adversary reaction here at the moment; I would be inclined to say at the moment, no, considering the nature of the policy. Well, I have two women waiting for me.

Simultaneous Discussion.